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EFFECTS OF METHYLPHENIDATE ON OPERANT BEHAVIOUR IN RATS: MODIFICATION BY PENTOBARBITAL AND RESERPINE

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a dissertation entitled "Effects of methylphenidate on operant behaviour in rats: modification by pentobarbital and reserpine", submitted by Samuel D. Dalrymple in partial fulfillment of the requirements for the degree of Master of Science.

ABSTRACT

The effects of two drugs, methylphenidate and pentobarbital on the behaviour of rats trained to respond on a tandem fixed interval, fixed ratio schedule of reinforcement were investigated. The effect of methylphenidate was found to be similar to that of the amphetamines previously reported by other workers. It tended to enhance response rate where the schedule component generated a low rate of responding, and to depress a relatively high response rate. Pentobarbital tended to increase rate of responding where a high response rate was already established, but had little effect on the low interval component rate.

In phase II of the study, the effects of simultaneous administration of the two drugs was studied. An enhancement of the methylphenidate effects by pentobarbital was evident at lower dosage levels (2.5 and 5 mg. per Kg.) but the 10 mg. per Kg. dosage tended to mask this effect. It is emphasized that this modifying influence appeared to be reciprocated, and the detailed effects of each dosage combination are discussed.

The third experimental phase involved an analysis of the effects of methylphenidate on behaviour after chronic pre-treatment with reserpine. Methyphenidate attenuated the behavioural blocking effect of reserpine, this being directly proportional to increasing dosage.

As previous workers have found, schedule controlled behaviour is differentially sensitive to the effects of psychoactive drugs; the present findings are consistent with this functional generalization.

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INTRODUCTION

Since the mid-1930's, the growth of interest of behavioural scientists in psychopharmacological agents has resulted in the development of a new sub-discipline within the framework of Psychology. While it was concerned initially, with the possible utility of new drugs in the psychiatric field, behavioural pharmacology has now broadened to include the most general problems of the action of drugs upon behaviour.

One of the great problems in the analysis of drug-behaviour relationships, lies in the considerable differences between individuals in their reactions to a drug at a given dosage. One solution to this problem involves the intensive study of individual subjects, and, as this is a common feature of operant conditioning techniques, the latter have been employed, in this field, with considerable success.

Basically, the conceptual framework for such comparative experimental analyses rests upon a single principle, namely that the characteristics of an organism's behaviour are, to a considerable extent, determined by what the environmental consequences of that behaviour have been in the past. The term "operant behaviour" has been used to refer to behaviour

which operates upon the environment in this fashion.

The process of manipulating such behaviour as a function of its environmental consequences has been termed "operant conditioning." The ease of interpretation of the resulting data is enhanced by:

1) Selecting for measurement and manipulation a response that the organism can perform easily and immediately be in a position to repeat.

2) Selecting an environmental consequence, or "reinforcement" that is appropriate to the particular experimental animal.

3) Utilizing motivational levels that are strong enough to minimize the effects of many experimentally irrelevant variables.

4) Systematic limitation of the experimental environment to permit at least some reasonable degree of stimulus control and specification.

The operant approach typically involves a small number of experimental subjects and the emphasis is placed on close

observation and careful experimental control of the individual subject. Thus, in the psychopharmacological field, while the wide individual differences remain, the high degree of intra-subject constancy resulting from careful establishment of baseline behaviour furnishes a sound basis upon which a variety of drugs and dosages may be evaluated.

However, operant techniques have not remained simply a tool of the behavioural pharmacologists; an important branch of research is now concerned with the effects of various drugs on specific components of various schedules of reinforcement. Boren (1966) has discussed this area of research, and presents the following rationale for this work:- "A drug can occasionally be found which either has a specific effect or at least has a main effect that is not seriously disrupted by secondary effects. This drug can then be used as an analytical tool. For example, Dews (1958) showed that behaviour maintained by a fixed interval (FI) schedule of reinforcement was much more sensitive to pentobarbital than was behaviour maintained by a fixed ratio (FR) schedule. Herrnstein and Morse (1956) examined the effect of the same drug with similar values of a tandem FI FR schedule, where the behaviours generated by the two components of the schedule were joined in a single performance and could not be easily disentangled. However, when pentobarbital was given in a high dosage, the post-reinforcement pause characteristic of

ratio behaviour remained. Thus, the drug experimentally separated the two behaviours and gave the experimenters additional evidence that the complex tandem performance could indeed be properly analyzed into the single components."

Of late, the work in this area has become subdivided to a certain extent, into a field concerned primarily with the effects of barbiturates, and a second field dealing with amphetamines and allied drugs. The work reported in this thesis has a fourfold purpose:

1) To examine the effects of a psychomotor depressant drug, pentobarbital on fixed interval and fixed ratio behaviour.

2) A similar investigation into the effects of Methyl phenidate - a psychomotor stimulant.

3) An examination of the synergistic effects of both drugs in a selection of specified dosages.

4) An examination of the antagonistic effects of meyhlyphenidate and reserpine following chronic administration of latter.

When an organism acts upon its environment, the changes induced in that environment often affect the organism itself. Some of these changes are directly beneficial to the organism in that they may make a direct contribution to its survival or are rewarding in some other way. These changes are then known as reinforcers: when they follow a given behavioural act, they increase the likelihood of its subsequent repetition. The two important functions of reinforcement are a) that it induces a relatively stable pattern of behaviour, and b) that given adequate control, it maintains this behaviour almost indefinitely. Since the early 1930's, there has been active interest in the various ways in which reinforcing events can be programmed. It was soon recognized, of course, that a given behaviour pattern of an organism in its natural habitat, seldom has the same effect upon the environment in two instances, and the kind of effect called a reinforcement is seldom inevitable.

In other words, continuous reinforcement of a behaviour pattern is rare, whereas intermittent reinforcement is usually the rule.

In 1933, Skinner reported experiments in which reinforcements were intermittent and in 1938, pointed out that they may be scheduled in many ways, with subtle differences in scheduling generating dramatic differences in behaviour. A

schedule of reinforcement is defined, not in terms of its effect upon behaviour, but rather, in terms of either the time elapsed since the preceding reinforcement or number of responses required in order for the organism to obtain a reinforcement. These two possibilities yield four basic schedules:-

1) Fixed interval (FI):- The first response after a given time interval has elapsed yields a reinforcement.

2) Variable interval (VI):- Similar to fixed interval except that reinforcements are scheduled according to a random series of intervals having a given mean. A variable interval schedule is stated in terms of the average interval of reinforcement.

3) Fixed Ratio (FR):- A response is reinforced upon completion of a fixed number of responses counted from the preceding reinforcement.

4) Variable Ratio (VR):- Similar to a fixed ratio except that reinforcements are scheduled according to a random series of ratios having a given mean.

Of the possible combinations of the above schedules, the one that was selected for this work is known as a Tandem FI FR

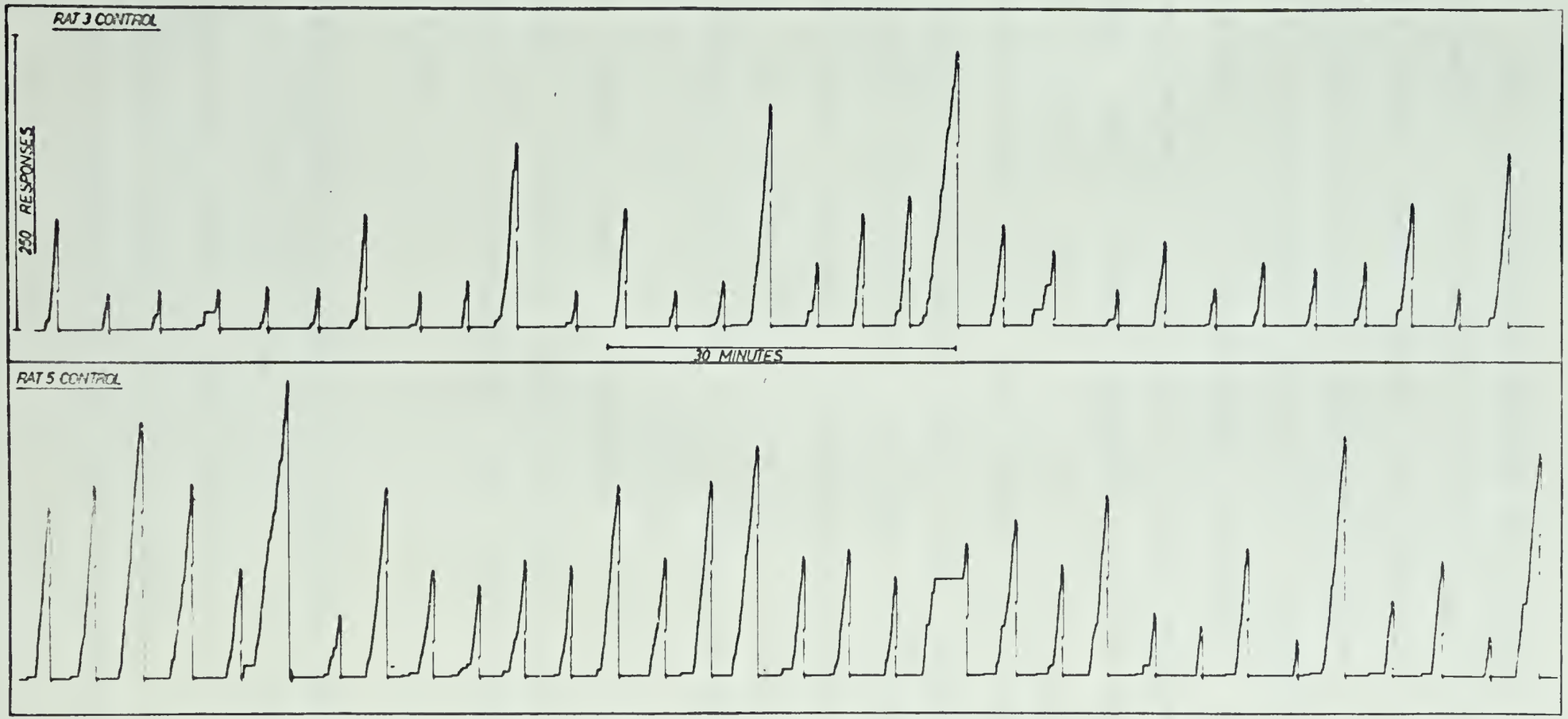

FIGURE 1

Samples of cumulative records, obtained during control sessions, showing performance on the Tandem FI4 FR 30 schedule of reinforcement.

schedule. This is defined by Ferster and Skinner in the following manner:- "A schedule of intermittent reinforcement in which a single reinforcement is programmed by two schedules acting in succession without correlated stimuli, e.g. in tandem, FI 10 FR 5, a reinforcement occurs when 5 responses have been executed after a 10 minute interval has elapsed. Both contingencies must be met consecutively for every reinforcement that is obtained. Such a schedule generates certain characteristic behaviour patterns. Typically, a given reinforcement is followed by a period during which the organism does not respond at all, this is the post-reinforcement pause. After frequent exposures to the schedule contingencies, this pause is extended further into the interval component. At some point during the interval component, the organism starts to respond at a low rate, and this is gradually accelerated until towards the end of the interval, and during the ratio requirement, it is responding at a very high rate which is maintained until the reinforcement is delivered. A cumulative record provides an excellent representation of such behaviour, and a typical example is shown in Figure I.

The development of tandem FI FR behaviour has been reported in detail by Ferster and Skinner (1957). Using food deprived pigeons which had previously been stabilized on FI 45 as subjects, they established a tandem FI 45 FR 10 schedule. The required response was the pecking of a key, and a food reinforcement was

Fig. 503. Segments from third through sixth sessions of Hand M. 45 FR 10

Fig. 504. Segments from the 21st to 24th sessions of Hand [illegible] FR 10

FIGURE 2

Cumulative records showing the development of behaviour patterns generated by a Tandem schedule of reinforcement

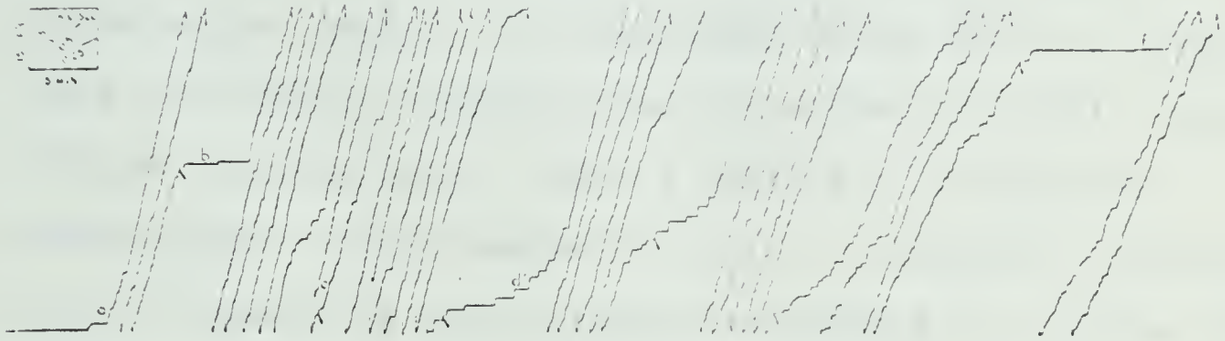

Fig. 505. Tand FI 45 FR 10 after 290 hr

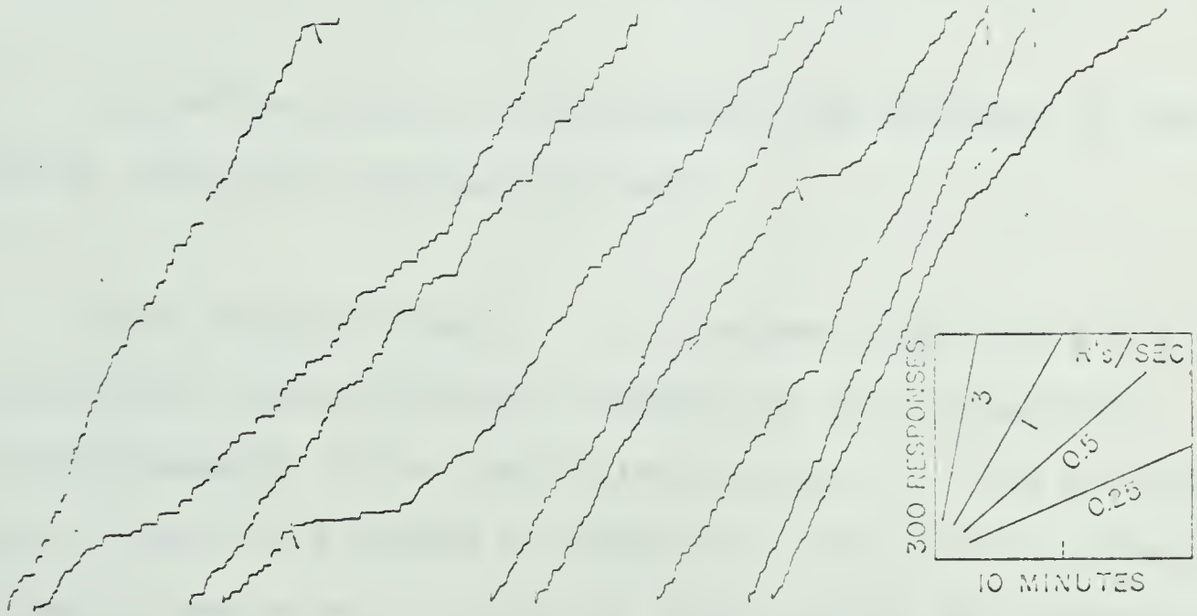

Fig. 506. Continuation of Fig. 505

FIGURE 3

Cumulative records showing the development of behaviour patterns generated by a Tandem schedule of reinforcement

used. During the first session, there was a low overall response rate of approximately 0.2 response per second, and the cumulative record showed an irregular trace. In the second session, the cumulative trace showed a step-wise character due to short bursts of responding at about 3.5 responses per second. The scalloped trace which is characteristic of interval behaviour had not appeared at this stage. Fifteen sessions later, after a total of 170 hours of reinforcement on the tandem FI 45 FR 10 schedule, the overall rate of responding had increased considerably, and the interval scallop had become prominent. (See Figures 2, 3).

A similar course of development was observed in the early stages of the present study.

From Figures 1 and 3, it is evident that there are three fairly well defined stages between any two consecutive reinforcements in the cumulative record:- 1) The post-reinforcement pause, 2) a period of responding at a low but gradually accelerating rate, 3) a period during which the response rate is high and is maintained at this level until the next reinforcement is obtained. It is the possibility of studying such segments of a behaviour pattern that has drawn the attention of psychopharmacologists, the rationale being that such segments will be differentially sensitive to certain drugs.

This is the underlying orientation of the literature reviewed in the following section.

REVIEW OF LITERATURE

Psychopharmacology is concerned with the effects of drugs on the more or less intact animal. The major problem facing experimental work in this area is the complexity of behaviour. However, in view of the fact that Physiologists successfully study physiological drug effects by investigating their influence on a given system or even a group of cells, there would appear to be no valid objection to the psychopharmacologist studying the effects of drugs on behaviour in a similarly analytical way. One method of doing so is to study the frequency of occurrence of a given response (i.e. a "bit" of behaviour, not necessarily "to" something; it may be emitted "spontaneously"). It is convenient to select for study, a response whose occurrences can be recorded objectively, and which the animal can perform repeatedly over a period of time, e.g. rats pressing a lever; pigeons pecking a key; primates pressing push-buttons etc.

Many drugs have been shown to influence the rates with which animals make responses of this kind. The effects of a given drug dosage depend on four classes of factors:-

1) Genetic factors:- the species of the animal, and the particular individual chosen.

2) The nature and frequency of the response under experimental conditions

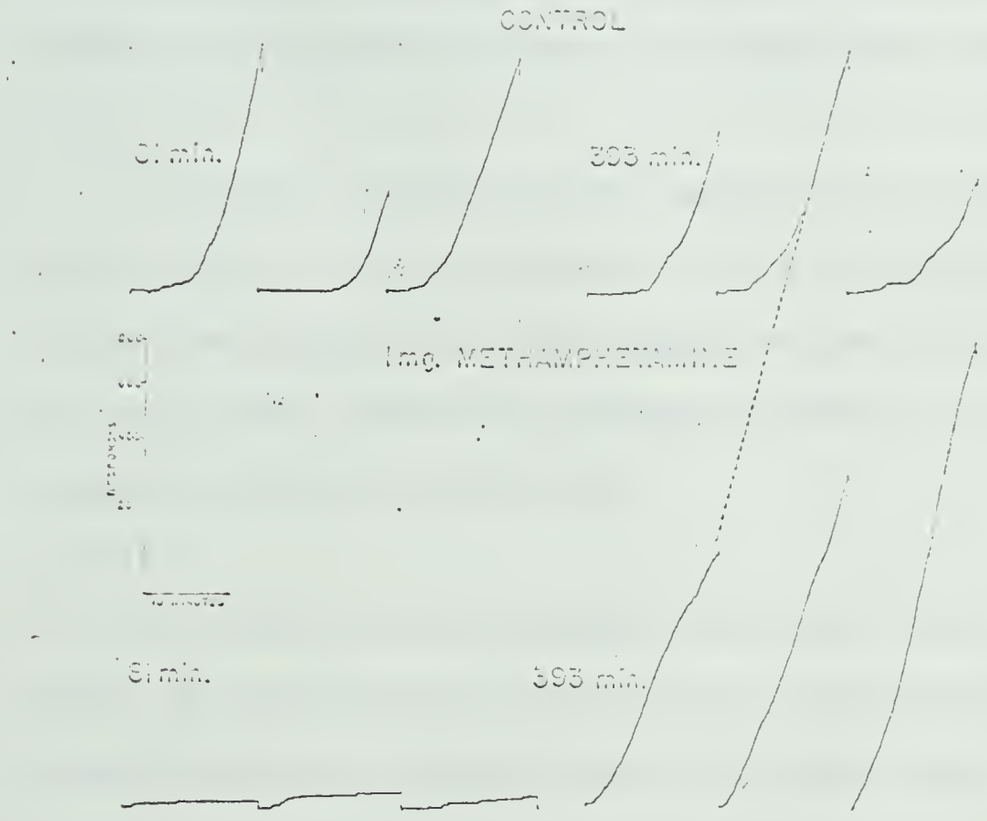

Fig. 1. Effect of methamphetamine on fixed interval performance in the pigeon. *Ordinate:* cumulative number of responses. *Abscissa:* time with key light on. The pen reset to the base line at each reinforcement. The figure shows samples of the performance in two periods during the daily session. Note the initial 'depressive' effect of the large dose of methamphetamine. The dotted line was added to show that the maximum rate following methamphetamine did not exceed the maximum control rate.

FIGURE 4

Sample of cumulative records obtained from pigeons performing on a fixed interval schedule of reinforcement.

3) The nature of the environment:- the eliciting, reinforcing and discriminative stimuli.

4) The previous history of the animal in terms of the training procedures employed and administration of drugs leading to possible adaptive or cumulative effects.

In order to clarify the nature of the work being carried out in this field, an example would be appropriate at this stage. A good representative experiment is one reported by Dews in 1958, in which the effects of methamphetamine on Fixed Interval behaviour were investigated.

A pigeon was maintained on partial food deprivation, and, after being trained to peck at an illuminated plastic key, was given access to the key for a few hours each day.

The interval requirement was then gradually introduced, until after several sessions, a stable behaviour pattern at FI 15 minutes had emerged. Thus, the animal was required to wait 15 minutes, and then to peck the key once after which a food reinforcement would be presented for 4 seconds. A typical behaviour pattern is generated by this schedule, a sample of which is shown in Figure 4(a). These curves should be compared with those shown in Figure 4(b), which were obtained from the same animal following the administration of a dosage of 2 mg.

per Kg. of methamphetamine.

Dews found that the characteristic effect of methamphetamine is to lead to an increase in the number of responses made per interval. However, the maximum rate of responding is not increased, instead, the animal responds steadily at the beginning of the interval at a time when, under control conditions, there is little or no responding.

Since Dews' early work in this field, a considerable body of literature has accumulated on the effects of amphetamines on behaviour. Many other studies have shown that where animals are required to emit a given response in order to avoid shock, amphetamine tends to increase the rate of avoidance responding. Hearst and Whalen in 1963, analyzed this finding in some detail. They demonstrated that, in a discriminated avoidance situation where a warning signal precedes shock, a dosage of 3 mg./Kg. of d-amphetamine increased the number of shocks avoided. They also noted that the general topography of the animals behaviour was affected by the drug. For example, it showed less tendency to crouch when the warning signal was presented, and was, therefore, more likely to emit the required response. The authors further argued that since many studies have failed to show improved avoidance performance with increased shock intensities, the augmentative effect of amphetamine upon avoidance responding

is probably not a function of the drug increasing the aversiveness of the shock.

The influence of Amphetamines has also been studied in punishment and conflict situations. In 1956, Brady reported that the response rate of an animal during a stimulus paired with shock decreased under 2 mg./Kg. of amphetamine. Teitelbaum and Derks (1958) found that the effect of d-amphetamine varied with dosage. A dose of 0.5 mg. per Kg. tended to suppress response rates in the presence of the shock-paired stimulus, but increased the rates in the absence of that stimulus. With a higher dosage of 1 mg. per Kg. the animal responded continiously at high rates, both in the presence and absence of the stimulus. Geller in 1962, and Sidley in 1963 have presented evidence that lower rates of response under amphetamine result when the subject is punished. However, studies by Barry, Wagner and Miller (1962 and 1963) and Hanson et al (1964) have failed to confirm this finding. In general, this aspect of the field is poorly documented compared with the work on avoidance behaviour. However, theoretically it would be expected that similar results would be obtained under both conditions.

Kelleher and Morse in 1964 compared behaviour under shock-escape schedules with that induced by food reinforcement schedules and found that d-amphetamine (0.01 to 1 mg. per Kg.)

produced essentially similar effects upon response rate regardless of whether food reward or shock escape was programmed. An interesting additional finding was that the direction of the drug induced behavioural change varied as a function of the reinforcement schedule maintaining the behaviour. When fixed ratio contingencies are programmed, high doses of amphetamine decreased the response rate while fixed interval responding was accelerated. This phenomenon was further investigated by C.B. Smith (1964) who used a multiple Fixed Interval (300 sec.) - Fixed Ratio (33 responses) schedule to study the effects of d-amphetamine on interval and ratio behaviour. Such a schedule is defined by Ferster and Skinner (1957) in the following manner:- "Reinforcement is programmed by two or more schedules, alternating, usually at random, each schedule accompanied by an appropriate stimulus as long as the schedule is in force." Smith used pigeons as subjects, and each was exposed to a daily 90 minute experimental session. During this period, the subject was placed in an experimental chamber where it had access to an illuminated key, and was permitted to obtain 40 reinforcements. The key was transilluminated by a blue light during the ratio component, and by a red light during the interval component. The two schedule components alternated.

On a day when a drug was to be administered, d-amphetamine was injected 5 minutes prior to the experimental session for

that day. At least 3 days elapsed between any two consecutive injections.

The most important result to emerge from Smith's work was an indisputable confirmation of Kelleher and Morse's finding. d-Amphetamine increased rates of responding during the fixed interval component and had the opposite effect on the fixed ratio component. In fact, his results permitted him to make the more general statement that d-amphetamine tends to increase rates of responding during portions of a schedule characterized by low rates of responding (F.I.), and suppress response rates during the schedule component characterized by high rates of responding (F.R.). In addition, Smith found that the daily administration of reserpine 16 to 18 hours prior to the running of the schedule further modified the effects of d-amphetamine. He found that it further increased the response rate enhancement effect of d-amphetamine at low rates of responding, but that it blocked the ratio suppressant effect of the latter at high rates of responding and that the subject returned to the high response rate seen under control conditions in the absence of both drugs. However, he is cautious in his interpretation:- "Whether this drug specifically enhances the rate increasing effects, antagonizes the rate suppressant effects, or otherwise modifies the effects of d-amphetamine, has not been determined."

The important points of the paper are that Smith was able to demonstrate that 1) Amphetamine modifies behaviour under certain schedules of reinforcement and 2) Both FI and FR schedules are sensitive to the drug. This second point is contrary to many previous reports of workers in this field, who have noted the apparent insensitivity of behaviour under FR schedules to modification of drugs. However, it is compatible with the report of Waller and Morse (1963) who found that FR behaviour was considerably affected by pentobarbital. Certain relatively low dosages consistently increased response rate under an FR 30 schedule, and higher doses produced decrement.

An examination of the literature in this field reveals that most of the work on psychomotor stimulants has been concerned with amphetamines. However, some studies have been devoted to the effects of caffeine, and, since its appearance in 1954, methylphenidate.

Since methylphenidate was one of the two drugs employed in the present study a detailed examination of its properties, as far as the literature permits, would be appropriate at this point.

Meier, Gross and Tripod (1954) were the first to investigate the central stimulating effects of this drug. Since they

were primarily concerned with the pharmacology of the drug, their findings concerned with its influence on behaviour were somewhat limited, however, they form a useful introduction to the psychopharmacology of the drug.

As expected, the authors found that increased motor activity resulted from administration of the drug. It was expressed in the experimental animals, as a general restlessness, and particularly, as a co-ordinated increase in motility; a tendency to move about and run, also to eat or gnaw, without becoming aggressive. Depending on the animal, the species and mode of administration, this central stimulating effect appears after doses of 0.5 to 1.5 mg. per Kg., lasts for several hours and then subsides, leaving signs of fatigue. Larger doses of methylphenidate produce an atactic gait and clonic tonic convulsions. In mice, the authors demonstrated that methylphenidate produced a fourfold increase in spontaneous activity (measured by the spring cage method) in doses of 2 mg. per Kg. administered sub-cutaneously, or 15 mg. per Kg. administered orally, and in this respect, it was indistinguishable from amphetamine. Using rats in an activity wheeel, it was satisfactorily demonstrated that methylphenidate (10 mg./Kg.) increases co-ordinated running movements. With higher mammals, lower dosages of methylphenidate often had a stimulating action on psychomotor activity. Thus dogs, 10 minutes after an intravenous

injection of 1 mg. per Kg. exhibit a marked restlessness, run around, and make many tic-like movements of the head. Both respiration and heart rate are accelerated, and during the next half hour, the animal is continuously moving, pants and shows increased salivation. The effects of the drug gradually subside over 3 or 4 hours. While there were individual differences in degree of activity at the 1 mg. per Kg. dosage, all subjects displayed increased activity at 2mg.per Kg. dosage even though the duration of the effect was only slightly prolonged.

The authors further investigated the effectiveness of methylphenidate in counteracting anaesthetic dosages of barbiturates. They found that it was effective against Pentothal, but was unable to rouse the subject from the anaesthetized state induced by any other barbiturates although it did counteract the respiratory depressant effect of morphine. Amphetamine had similar, but more marked effects in this experimental set-up. Meier et al reached the general conclusion that methylphenidate more closely resembles Caffeine in its effects, "and must be classified somewhere between Caffeine and d-amphetamine sulphate."

The problem of distinguishing between these psychomotor stimulants was approached by Mechner and Latranyi (1963) by way of operant behaviour procedures. Using rats that had

been trained immediately prior to the start of the experiment to perform consistently on both a fixed interval and a fixed ratio schedule, they were able to distinguish, accurately, the three closely related psychomotor stimulants, caffeine, methamphetamine and methylphenidate.

Four behavioural procedures were used, but only two are of direct importance to the present study, namely, fixed interval and fixed ratio, since these proved to be the best discriminators of differences between the behavioural effects of the three drugs. Under the fixed interval schedule, the subject was required to manipulate two bars; a response on bar A initiating a 30 second fixed interval and the first response on bar B following the end of this interval being reinforced. Typically, the subject paused after starting the interval, then began to respond on bar B, the response rate gradually accelerating until a reinforcement was obtained. It was immediately evident from the results, that in spite of wide individual differences, administration of each of the drugs resulted in an increase in the number of responses to bar B. However, Caffeine was much less effective in this respect than methamphetamine and methylphenidate and this difference was shown to be statistically highly significant. Further, at higher dosages of 12 and 24 mg. per Kg., Caffeine did not produce destruction of the temporal discrimination as did the remaining two drugs.

When the subject was required to perform under the fixed ratio schedule, it was again presented with two levers. 46 responses to bar A were required before a response to bar B would be reinforced. As in the fixed interval procedure, premature responses to bar B did not reset the count, but were also not reinforced. The subject typically completed a large number of the bar A responses before making a bar B response which was usually premature. Following the first bar B response, the subject normally alternated between A and B until the reinforcement was obtained, with an increasing number of bar B responses as the end of the ratio requirement approached. A post reinforcement pause was normally observed and again, wide individual differences were apparent. All three drugs increased the number of responses to bar B, but in this case, the effect was less marked under methamphetamine than with caffeine or methylphenidate. The three drugs were thus quite clearly distinguished; fixed interval isolates the caffeine effect, and fixed ratio, methamphetamine.

At the peak of its dose response curve, methylphenidate had behavioural effects very similar to methamphetamine under the fixed interval schedule and behavioural effects similar to those of caffeine under fixed ratio.

As will become apparent later, these results are of

considerable importance to the present study which employed a schedule with both interval and ratio components.

Having surveyed the literature concerned with psychomotor stimulant drugs relevant to the present study, the following section will deal, in a similar manner with psychomotor depressant drugs.

The term "psychomotor depressant" as applied to a given drug, suggests that the drug invariably causes a reduction in motor activity when administered to an organism. In recent years, psychopharmacologists have shown that this is not the case, and have further established that the behavioural effects of a psychomotor depressant drug are considerably influenced by the nature of the situation in which the subject is placed. The same point can also be made for psychomotor stimulant drugs, and the whole issue has been discussed in some detail by Morse (1962):- "In recent years, dramatic demonstrations of differential sensitivity to a drug in different situations have helped to establish the importance of environmental variables in determining the behavioural effects of drugs. But, since the selective modification of behaviour by drugs is the rule rather than the exception, the problem for behavioural pharmacology today is to go beyond the mere demonstration of differences. It must systematize and clarify the nature of the interactions between the effects of drugs and environmental determinants of behaviour.

A first step is to isolate and specify more exactly which environmental variables are most important in influencing the action of a drug on behaviour." As is evident from the preceding section, among the best demonstrations of this dependence of drug effects on environmental factors, are those that have employed operant techniques where the environment is, of course, very rigidly controlled. These methods were employed by Herrnstein and Morse (1956) in their investigation of the effects of barbiturates on behaviour. Dews (1955) had previously shown that the effects of sodium pentobarbital on a learned response in pigeons depend on the schedule of reinforcement used to maintain the response.

Herrnstein and Morse confirmed Dews' findings by use of a tandem schedule where both fixed ratio and fixed interval requirements had to be met in order for the subject to obtain a food reinforcement. Such a schedule combines features of both fixed interval schedules which generate relatively low rates of responding, and fixed ratio schedules which generate high response rates. The authors demonstrated that behaviour under the fixed interval component shows great sensitivity to sodium pentobarbital whereas behaviour under the fixed ratio component was relatively resistant to the drug. As the authors conclude: "These findings serve the dual purpose of further substantiating the selective action of sodium pentobarbital, and of being a demonstration of the presence of fixed interval and fixed ratio components within

the tandem schedule performance." Further evidence tending to confirm these results was obtained by Morse in 1962. Using a positively (food) reinforced multiple fixed ratio (30 responses) fixed interval (5 minutes) schedule, and pigeons that had reached a relatively stable level of performance on this schedule, he injected 3 mg. of pentobarbital sodium midway through an experimental session. Morse found that under non-drug conditions the subject typically responded at a steady, high rate during the ratio component, and during the interval component showed an initial pausing and then began to respond more and more rapidly until it reached a steady terminal rate. However, following the intramuscular injection of pentobarbital, there was a drastic reduction in the response output under the fixed interval condition, and little or no suppressing effect under the fixed ratio condition.

There is little doubt that the inter-relationship between drug effects and environmental variables is an extremely sensitive one. In fact, the differences generated by different schedules appear relatively gross when compared with similar differences that may be observed within the same type of schedule. Again, Morse has been an active investigator here. He used two different parameter values of fixed ratio reinforcement such that under one condition the subject was required to make 33 responses, and under the other, 330 responses in order to obtain

a reinforcement. Under non-drug conditions, the average number of responses per 10 minute period was found to be about twice as high on FR 33 as on FR 330. Following an intramuscular injection of sodium amobarbital (2.5 mg./Kg.) the response rate was almost the same under both conditions. This represents a negligible increase in response output under FR 33, but a substantial one under FR 330. With a dosage of 10 mg./Kg., Morse found a 39 percent decrease in response output on FR 33 and an increase in response output on FR 330 of 84 percent. Further similar experiments have confirmed Morse's finding that the less well maintained of two performances was less depressed by moderate (sub-anaesthetic) dosages of amobarbital. That this is a basic and generalizable phenomenon was demonstrated by Verhave who followed the Herrnstein and Morse report (cited above) with a similar experiment involving the use of monkeys on a multiple fixed interval, fixed ratio schedule. He was interested in the effects of secobarbital on the behaviour patterns generated. He found as did his predecessors in this field, that behaviour on a fixed interval schedule (or component) is more sensitive to the effects of a barbiturate than fixed ratio behaviour. In addition, he showed that the effect of a barbiturate can be described in three phases:-

1) An initial, brief, stimulant phase.
2) A period of overall depression.
3) A post depression excitatory phase.

This finding has an important bearing on the present study as will be seen in the section of the results dealing with the synergistic effects of a psychomotor stimulant and a psychomotor depressant.

In this final section of the literature review, the research focussing on the effects of two drugs administered simultaneously, or in close succession, will be dealt with.

In 1957, Tripod reported that the increase in random, motor activity in mice, produced by Amphetamine, was enhanced by the concurrent administration of atropine. This was among the first of several important demonstrations of the modification of the behavioural effects of one drug by the presence within the subject, of another. Carlton and Didamo (1960) reproduced this phenomenon in rats, and examined it in greater detail. They used 5 male albino rats that had received extensive training on a Sidman non-discriminated avoidance schedule. This schedule may be described as follows: The subject is placed in an experimental chamber with a grid floor through which shock may be delivered, and a lever which the animal may press to avoid shock. The procedure is to give the subject a brief (0.5 sec.) shock whenever X seconds elapse without a response (shock - shock interval); each lever press by the animal postpones the shock for Y seconds (response - shock interval).

Carlton and Didamo employed shock-shock and response-shock intervals of 20 secs. each. Experimental sessions were 5 hours in length, and drugs were administered after 1 hour of the session had elapsed. As expected, Amphetamine administered intraperitoneally in dosages ranging from 0.25 to 2.0 mg. per Kg. increased the rate of lever pressing to avoid shock. Equimolar dosages of atropine were uniformly ineffective in increasing the rate of avoidance responding and had, if anything, a slight tendency to depress response rate. However, each one of these dosages of Atropine had a marked augmentative effect on the increases in rate caused by am amphetamine injection if administered at the same time as the latter. The duration of the increased rate caused by amphetamine was also extended. Subsequently, in 1961, Carlton was able to demonstrate very similar effects with Scopolamine; ineffective alone, but augmenting the effect of amphetamine to a considerable degree.

These were among the earliest of the studies designed to investigate synergistic effects of drugs on specific behaviour patterns. Smith (1964) was able to reproduce the general findings of Carlton et al using pigeons, and Reserpine instead of Atropine. In addition, the subjects were on a multiple fixed interval, fixed ratio schedule involving positive reinforcement. The major results of this experiment have already been discussed in the section dealing with psychomotor stimulants, but it is perhaps more meaningful to discuss at this stage, Smith's finding on the

antagonistic effects of d-amphetamine and reserpine.

He injected 0.1 mg./Kg. reserpine daily, for 7 days prior to, and during the d-amphetamine study. The injections were made 16 to 18 hours prior to the beginning of each experimental session. He found that it further increased the response rate enhancement effect of d-amphetamine at low rates of responding (fixed interval component), but that it blocked the ratio suppressant effect of the latter at high rates of responding (fixed ratio component). In effect, the subject returned to the high response rate seen during the ratio component under control conditions, and in the absence of both drugs. As already mentioned, Smith was not prepared to make any pronouncement on the mode of interaction of the two drugs. It should also be noted at this stage, that Davis (1965) has confirmed that the rate decreasing effect of d-amphetamine on ratio schedules can be off set by a psychomotor depressant, in this case, chlorpromazine.

More germane to the present study from the point of view of drugs employed, is the work of Weiss and Laties (1963), particularly their investigation of the combined effects of amphetamine and pentobarbital. The dogs which were used as subjects, were trained to press a small disc with the nose; the actual duration of "nose pressing" being the important variable. On accumulation of 60 seconds of "nose pressing", a food

reinforcement was delivered. Number of responses (i.e. contacts of nose and disc) was also recorded. Both amphetamine (.25 to 1.0 mg./Kg.) and pentobarbital (2.0 to 16.0 mg./Kg.) increased responses per reinforcement and rate of responding, but when injected together, the effects were striking. A mixture of 0.5 mg./Kg. of amphetamine and 16 mg./Kg. pentobarbital increased the number of responses per reinforcement by 34 percent over and above the sum of the responses emitted under each of the drugs acting individually. The number of responses was 10 times as great as that following a saline injection.

As will be seen from the following section on Experimental design and Method, the drugs employed in the present study were a psychomotor stimulant, methylphenidate and a psychomotor depressant, pentobarbital. From the preceding literature, it would be expected that in addition to the general increase in motor activity induced by methylphenidate, both an increase and a decrease in motor activity may be anticipated in the case of pentobarbital, depending upon the drug dosage and the behavioural schedule employed.

The remaining area to be reviewed in this section is that dealing with the antagonistic effects of psychomotor stimulants and a specific psychomotor depressant; reserpine. The behavioural effects resulting from the administration of reserpine

alone have been well documented and no attempt has been made to reproduce them in the present study which is concerned only with the effects of reserpine and methylphenidate acting together.

Cole and Glees (1957) made a detailed examination of the gross behavioural changes produced in monkeys given reserpine alone, and reserpine followed by one of its antagonists methylphenidate. Briefly, the authors found that the effects of reserpine alone following a 5 mg. per Kg. dosage are a drop in body temperature of up to 6° centigrade, decrease in respiration rate, and increase in pulse rate. The subject adopts a "foetal position", and finally, a catatonic like state appears in which the animal can be placed in and will maintain bizzare positions. They also found that a period of aggressive confusion occurs both during onset of and recovery from the effects of the drug. Aggressive responses to threats from another monkey persist, but movements are much slower. The authors report that following an injection of methylphenidate, the effects of reserpine are completely abolished, occulomotor co-ordination is completely restored (shown by the subject's ability to jump from one side of the cage to the other), and spontaneous activity reappears.

More detailed work on the different effects of a psychomotor stimulant and reserpine within the operant conditioning framework

has been reported by Sidman (1956). While Sidman did not study the antagonistic effects of the two drugs, his work serves to highlight the differences between them. Using amphetamine as the psychomotor stimulant, and rats as subjects, he studied the effects of the two drugs on a D.R.L. (differential reinforcement of low rates) schedule. This is defined by Ferster and Skinner in the following manner:- "Reinforcements occur only when the rate of responding is below some specified value." In Sidman's experiment it was required that in order for a response to be reinforced, 20 seconds must have elapsed since the preceding response. In addition, a second lever was present in the experimental chamber, to which the subject was required to respond when an auditory stimulus was presented; the animal's response to this lever also turned off the stimulus. Thus, the schedule employed was, in effect, a combined D.R.L. and simple discrimination schedule. The subjects were deprived of water, and a drop of water, presented after an appropriate response, acted as reinforcement. The schedule programme was arranged to minimize interaction effects between the two levers, thus, with this procedure, simultaneous auditory and temporal discriminations are built into the animals behavioural repertoire. Following adminstration of amphetamine, an increase in response rate was observed on both D.R.L. and the discrimination components. The temporal discrimination was somewhat disrupted due to this higher response rate, with fewer 20 second pauses between the responses.

The auditory discrimination remained, but many more inappropriate responses to the second lever were given in the absence of the stimulus.

Under chronic reserpine administration (0.2 mg./Kg. 3 to 4 hours after each experimental session) no striking effects were noticed over the first two weeks. Thereafter, a marked deterioration in the temporal discrimination was observed. However, the stimulus discrimination appeared to be relatively unaffected with respect to frequency of extra responses and latency of responses to the stimulus. Thus reserpine, unlike amphetamine, produces a differential effect upon time and stimulus discriminations. Under an avoidance schedule, the animal received a shock every 20 seconds unless it pressed the lever, in which case, shock was delayed for 20 seconds from the moment of response. When a dosage of 3 mg. per Kg. of amphetamine was injected, the rate of avoidance responding increased and the time discrimination was affected in much the same way as in the D.R.L. procedure. Under a reserpine dosage, similar to that described above, response rates declined rapidly, the avoidance behaviour being suppressed by the drug.

The actual antagonistic effects of reserpine with a psychomotor stimulant have been studied by Rech (1964). He trained 110 female rats to conditioned avoidance in a shuttle

box, using a 600 cycles per second tone as the conditioned stimulus which preceded shock by 5 seconds. The subjects were required to reach a 50 percent successful avoidance performance before drug treatments were started. The drugs employed were reserpine and d-amphetamine. A dosage of 2 mg. per Kg. of reserpine was injected, and the subjects were tested at 2.5, 8, 24 and 48 hours afterwards. Immediately after each of these sessions, 2 mg. per Kg. of d-amphetamine was administered, and the subjects again tested 30 minutes thereafter. Cumulative effects from the repeated amphetamine dosages were not expected, since the drug is metabolized relatively rapidly and no trace of it is found in the brain approximately 4 hours after intraperitoneal injection. The behavioural effects of reserpine were completely abolished by the amphetamine and performance was enhanced up to 8 hours after reserpine administration. However, when amphetamine was injected at the 24 and 48 hour stages, performance again deteriorated due to the hyperactivity induced by the amphetamine, the effects of reserpine being less potent at this stage. With a dosage of 0.5 mg. per Kg. of amphetamine, maximum antagonistic effects against 2 mg. per Kg. reserpine were observed 24 hours following the administration of the latter; l-amphetamine was also tested under similar experimental conditions and found to be less effective than the d-form in counteracting the effects of reserpine. The author suggests that this difference may be

related to the lesser potential of l-amphetamine for releasing brain nor-epinephrine.

Finally, it will be recalled that in the preceding review, a paper by C.B. Smith has been mentioned. While primarily concerned with the behavioural effects of d-amphetamine, he also found that reserpine modified these effects in a highly specific manner. Since his is possibly one of the most detailed and accurate reports on the combined effects of these two drugs, his findings are worth recall in the present context. While Smith, as already stated, was cautious in his interpretation of these effects, this experiment remains one of the clearest demonstrations of the influence of environmental variables in determining the manner in which a given drug (or drugs) will modify given behaviour patterns.

The preceding review has, of necessity been highly selective, including only research findings which have an immediate bearing on the present study. In addition the pharmacological literature concerning the drugs to be used, has not been treated in detail; however, comprehensive reviews of the pharmacology of methylphenidate (Kreuger and McGrath, 1964), reserpine (Schlittler and Plummer, 1964) and the barbiturates (Goodman and Gilman, 1955) are readily available.

METHOD

Subjects

Four male albino rats (Wistar strain), approximately 140 days of age at the start of the experiment were used. Throughout the study, each subject was maintained at approximately 70 percent of its free-feeding weight. Water was freely available at all times in the home cages, but not in the experimental chamber.

Apparatus

The apparatus consisted of one sound resistant test chamber equipped with a lever and Gerbrands feeder which dispensed 45 mg. food pellets as reinforcement. Relay equipment and electronic timers automatically controlled the experimental contingencies. Behaviour was recorded by means of a Gerbrands cumulative recorder and a print-out counter. A drinkometer sensing head was connected to the lever such that every contact the animal made with the lever was recorded, thus giving information on the number of times the subject touched, but did not depress the lever. A digital counter recorded the total number of lever presses made during the session.

Procedure

Each subject was completely deprived of food for several days preceding the start of the experiments, until its weight had stabilized at approximately 80 percent of its free feeding weight.

On the first experimental day each animal was magazine trained. Since this, and subsequent procedures were the same for all subjects, the following discussion will refer to a single animal. Magazine training involved placing the hungry animal in the experimental chamber where a few food pellets were available in the food cup. When these had been consumed, the experimenter delivered a further pellet. A short pause followed to allow the subject to move away from the food cup before delivering another pellet. This procedure continued until the animal would return to the food cup whenever it heard the click of the pellet dispenser on delivery of a pellet. When this behaviour pattern was established, the training period entered the second phase. The subject was given a pellet only when it reared up on its back legs, then only when it reared in the proximity of the lever, and subsequently, only when it made closer and closer approximations to the lever press. When the subject was pressing the bar frequently, it was permitted to obtain a total of 100 reinforcements on a continuous reinforcement schedule (i.e. a

pellet was delivered following each depression of the lever). The subject remained on the schedule for 3 days. The third phase of the training period involved the introduction of the subjects to the tandem FI, FR schedule. This is defined by Ferster and Skinner as :- "A schedule of intermittent reinforcement in which a single reinforcement is programmed by two schedules acting in succession without correlated stimuli. E.G. in tandem FI 10 FR 5, a reinforcement occurs when 5 responses have been executed after a 10 minute interval has elapsed." From the commencement of this stage through to the end of the experiment, experimental sessions for all subjects were 3 hours in length, and 21 hours elapsed between consecutive sessions for each animal. In order to establish the tandem schedule of FI 4 minutes FR 30 responses, the subjects were gradually shaped through the following stages commencing on the fourth experimental day.

FI component	FR component	Time spent on each stage
30 seconds	5 responses	3 days
60 seconds	10 responses	2 days
100 seconds	20 responses	2 days
100 seconds	25 responses	1 day
100 seconds	30 responses	16 days
180 seconds	30 responses	7 days
200 seconds	30 responses	1 day
220 seconds	30 responses	1 day
240 seconds	30 responses	Final parameters

As already stated, these final parameters were selected since they resulted in behaviour patterns in which interval and ratio components, and post-reinforcement pausing were easily distinguishable. All subjects remained on the FI 4 minutes FR 30 responses schedule for 41 days by which time they had attained the criterion of stability. This criterion is one that was employed by Schoenfeld, Cumming and Hearst (1956) and is described by them as follows:- "The first seven days on any schedule are not considered in computing stability. For the next six days, the mean response rate per minute of the first three days of the six is compared with that of the last three days; if the difference between these means is less than 5 percent of the six days' mean, the animal is considered to have stabilized. If the difference between sub-means is greater than 5 percent of the grand mean, another experimental day is added and similar calculations are made for that day and the 5 days immediately preceding it. The process is continued until the criterion is met." It should be noted that both in the 1956 paper, and in a subsequent report by Cumming and Schoenfeld (1960), the authors reported that the criterion was not entirely satisfactory, since fluctuation beyond the 5 percent limit was noted in many subjects after they had fulfilled the requirements of the criterion. However, since it is the only method other than visual inspection of cumulative records, that offers any indication of the subjects approach to stability, it was employed in the present

study.[1] Forty-one days were required for the animals to reach criterion performance on the final parameters, and drug tests commenced on the 74th day of the experiment. Intraperitoneal injection of drug solutions was the mode of drug administration employed at all times in the present study. Three determinations were made of the behavioural effect of four dosage levels for the two drugs employed at this stage; methylphenidate[2] and pentobarbital,[3] and treatment was identical for all animals. The four dosage levels employed were 0.5, 2.5, 5.0 and 10.0 mg. per Kg. Over the first 12 days of drug administration, one determination was made for both drugs at each dosage level, and these were regarded as pilot data giving the experimenter some indication of the results to be expected. This was followed by 33 days during which the three determinations of each dosage level were made in a random sequence with 10 interspersed control days.

Upon completion of this stage, the experiment entered the phase dealing with the synergistic effects of methylphenidate and pentobarbital administered simultaneously 45 minutes after each drug session began. Three dosage levels of each drug were used, 2.5, 5.0 and 10.0 mg. per Kg., and three determinations of

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1. A full discussion of the problems associated with behavioural stability and their criteria is offered in "Tactics of Scientific Research" by Murray Sidman (1960); see also the Discussion.

2. The lyophilized hydrochloride salt of this drug dissolved in distilled water.

3. Pentobarbital Sodium in a solution of Alcohol (10%), Propylene Glycol (20%) and distilled water.

five drug dosage combinations were used, shown in the following table:-

Methylphenidate	Pentobarbital
10.0 mg. per Kg.	10.0 mg. per Kg.
5.0 mg. per Kg.	5.0 mg. per Kg.
2.5 mg. per Kg.	2.5 mg. per Kg.
2.5 mg. per Kg.	10.0 mg. per Kg.
10.0 mg. per Kg.	2.5 mg. per Kg.

The 0.5 mg. per Kg. dosage level for each drug was not employed since it appeared from the preceding phase, that the behaviour patterns and recording methods were not sufficiently sensitive to appreciate the relatively small influence of this low dosage on any of the higher ones. A similar argument applies to the fact that adjacent dosage levels were not employed.

Again, the treatments were administered in a random sequence, however, in this phase, each alternate day was a control session.

The final stage of the experiment was devoted to an examination of the antagonistic effects of methylphenidate and reserpine.[1] The latter was administered at a dosage of 0.2 mg. per Kg. for ten days prior to and each day throughout this phase immediately following each experimental session. Methylphenidate

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1. Dissolved in 1% benzyl alcohol and distilled water.

was injected on alternate days, 45 minutes following the start of the session, one of the following doses being administered:- 2.5, 5.0 or 10.0 mg. per Kg. Again, the dosages were injected in random sequence, each alternate day being a control session. Throughout the experiment, the volume of drugs, or control injections was held roughly constant.

In addition to the cumulative record, performance on the tandem FI 4 FR 30 schedule was recorded by means of a print-out counter. Three measures were obtained from the latter:-

1) Duration of post-reinforcement pausing (defined as the time elapsing between the delivery of a reinforcement and the fifth response following that reinforcement) in 0.5 second intervals.

2) Number of responses occurring in each of the twelve 20 second periods making up the 4 minute interval component.

3) Time taken to emit the 30 responses of the ratio component following the completion of the interval component. Again, this measure was in 0.5 second intervals.

As already stated, a drinkometer sensing head, attached to a digital counter, recorded all contacts of the subject with the lever. This, together with the print-out counter came into

operation 45 minutes after the start of each session, thus, only uncontaminated data on drug effects, and strictly comparable control data were recorded through these channels. A further digital counter recorded the total number of depressions of the lever made throughout the three hour sessions, and the cumulative recorder was similarly employed for the full three hours. In interpreting the records obtained from the latter, it should be remembered that the pen was automatically reset following each reinforcement obtained by the subject.

RESULTS

The material presented in this section may be classified under one of the following two sub-headings:- 1) General Trends, namely those emerging from visual inspection of the cumulative records, differences in number of responses made per session and variation in number of contacts with the lever per session recorded by the drinkometer sensing head. These results are reported in terms of the stabilized "baseline" behaviour patterns which followed the attainment of the Schoenfeld, Cumming and Hearst criterion of behavioural stability (see Method Section), and the major drug induced deviations from the baseline patterns. 2) Detailed Findings. Those results emerging from analysis of the print-out data. They fall into four categories: a) Response rate per minute, b) Time taken to complete the ratio requirement of the schedule, c) Post-reinforcement pausing, d) Calculation of indices of curvature. Again, the report is in terms of "baseline" behaviour and deviations from this following drug administration.

A further important point should be made at this stage before embarking on the results themselves. From the earliest stages through to the completion of the project, it was apparent that there were wide individual differences between subjects in terms of their performance on the schedule of reinforcement employed. There was, however, a high degree of intra-subject

behavioural stability, thus the results are most meaningful when interpreted in terms of individual subjects, however, general trends were revealed by statistical manipulation of the results of all the subjects.

As already stated in the Method Section, 41 days were required for the subjects to achieve behavioural stability, (according to the Schoenfeld, Cumming and Hearst criterion,) on the final parameters of the experiment. The subjects did not, of course, reach the criterion simultaneously as may be seen in Figure 5 . This graph shows the last 25 sessions of the stabilizing period. The last six points (open circles) plotted on each curve indicate the period during which each animal fulfilled the requirements of the behavioural stability criterion. Cumulative records of this period and those obtained from subsequent sessions when drugs were not administered indicate that the "baseline" behaviour remained highly stable for each animal. Figure 1 illustrated this point; it shows typical segments of the cumulative records of two of the subjects (rats 3 and 5) obtained during a control session (no drugs administered).

Of the drug treatments which commenced on the 74th day of the experiment, the data obtained over the first 12 days of drug administration were not included in the results presented here since they were regarded as pilot material. The results obtained

from the determination of the effects of pentobarbital and methylphenidate individually form the first major part of this section.

Inspection of the relevant cumulative records indicated that both pentobarbital and methylphenidate have little or no behavioural effects at the two lower dosages of 0.5 and 2.5 mg. per Kg. (Figures 6,9). The characteristic effects of the individual drugs appear at dosage levels of 5 mg. per Kg. It is evident from inspection of figure 9 that apart from the overall excitatory effect reflected in the increased response rate, methylphenidate also had a differential effect on the behaviour patterns of the two components of the schedule. Like d-amphetamine, it tends to enhance low rates of responding, and depress high rates of responding. Thus, in the present case, the post-reinforcement pause was abreviated, and the difference between response rates in the interval component and those in the ratio component was diminished.

Pentobarbital at the 5 mg. per Kg. dosage was shown by the cumulative record (Figure 7) to supress responding for a period immediately following administration. This period of supression showed considerable variation both between subjects and within the same individual and thus, could never be considered as a reliable measure of drug effect. However, the behaviour patterns emerging on recovery from the drug

effects showed high intra-subject constancy over the three determinations.

As Verhave reported, a post-depressive excitatory effect was apparent at this dosage level, being expressed as shorter post reinforcement pauses and an elevated response rate.

The 10 mg. per Kg. dosages produced similar, but more marked effects as registered by the cumulative recorders (Figures 8,11). Supportive evidence for these general trends was provided by differences in total number of responses, and number of contacts with the lever per session under control and drug conditions. The figures obtained by these methods had little value as measures of behavioural change since each was obtained from a complete session. Thus it is sufficient to mention that they contributed to the completion of the picture of the gross behavioural changes. An example here, was provided by the 10 mg. per Kg. dosage of methylphenidate. At this dosage level, it appeared from the cumulative record (Figure 11), that the subject had ceased to respond to the lever, this record being practically indistinguishable from that obtained under the 10 mg. per Kg. dosage pf pentobarbital. However, the number of contacts with the lever under the former conditions was very high, confirming that the subject was hyperactive, whereas when the latter conditions were operative, the subject was virtually anaesthetized, and very few contacts with the lever were registered.

Turning now to the synergistic effects of methylphenidate and pentobarbital; the cumulative records that were obtained following the simultaneous administration of 2.5 mg. per Kg. of each drug provide little indication that the behaviour patterns under these conditions differ in any way from those pertaining under control conditions. (See Figures 12 and 1). In the period immediately following injection of the drugs, the post-reinforcement pause appeared to be slightly abbreviated. The response rate during the interval component was somewhat elevated, however there is little apparent deviation from the control response rate during the ratio component.

The main effects of the combined dosage of 10 mg. per Kg. of methylphenidate and 2.5 mg. per Kg. of pentobarbital were clearly marked on the cumulative record (Figure 13). Immediately following injection of the drugs, the subjects ceased to respond on the lever. However, as in the case of the 5 mg. per Kg. and 10 mg. per Kg. dosages of methylphenidate above, the data obtained from the drinkometer sensing head indicated that this failure to press the bar was due to the subjects hyperactivity. This effect persisted for 30 to 40 minutes following injection. When lever pressing activity was re-established, the major features of the behavioural patterns (as compared with control behaviour) were 1) an almost non-existent post-reinforcement pause which generally lengthened as the drug effects diminished. 2) A considerably increased response rate during the interval

component. 3) A depressed response rate during the ratio component.

When the dosage values were reversed (i.e. methylphenidate 2.5 mg. per Kg. and pentobarbital 10 mg. per Kg. (Figure 14) there were no lever responses for a period following injection, however, in this case, the animal was in a somnolent condition due to the high pentobarbital dosage. When the subject again began to respond on the lever, the record shows an initial supression of post-reinforcement pausing. This was short lived, and the pause again became evident.

The increase in response rate during the interval component and the decreased response rate during the ratio component were also relatively short term effects but were more pronounced than was the case under the preceding conditions.

Perhaps the best illustration of the characteristic effects of each drug together with their synergistic influence appears under the 5 mg. per Kg. dosage of each (see Figure 15). The sub-anaesthetic effect of pentobarbital and the hyperexcitant effect of methylphenidate effectively counteracted each other thus shortening the time immediately following injection, during which the subjects failed to respond on the lever. As can be seen from the record, the duration of the pause in rat 5 was virtually non-existent. It would also appear that the

initial excitant effects of pentobarbital served to enhance those of methylphenidate to initially reduce post-reinforcement pausing to zero. A further marked effect was the increase in response rate during the interval component; an effect that persisted in the case of rat 5, throughout the remainder of the session, although of course, it was less pronounced as the influence of the drugs diminished. There was some reduction of response rate in the ratio component but this characteristic effect of methylphenidate was tempered by the pentobarbital and there is little sign of it 30 to 40 minutes after drug administration.

The final combination in this series was that of 10 mg. per Kg. of each drug. From Figure 16 it is apparent that in the period of cessation of responding on the lever immediately following injection the drugs tended to modify each other in terms of their behavioural effects. The period is considerably shorter than was the case under 10 mg. per Kg. of pentobarbital above, and more closely approximates the results obtained under the high methylphenidate dosage.

The high overall response rate which was maintained throughout the remainder of the session suggests that the post-depressive excitatory effects of pentobarbital enhanced those of methylphenidate. Post-reinforcement pausing was severely curtailed and in the case of rat 5, was non-existent

for a period following recovery of the lever response. Interval responding was enhanced, and remained high for the rest of the session, while depression of response rate during the ratio component was fairly rapidly dispelled.

Finally, in this section of the results, the cumulative record evidence obtained following the administration of reserpine, and the antagonistic effects of reserpine and methylphenidate will be reported.

As stated in the Method Section, each animal received a daily injection of 0.2 mg. per Kg. of reserpine. This psychomotor depressant has prolonged effects which may be apparent up to 72 hours after administration. The result of chronic administration was a gradual decrease in the number of lever responses until by the tenth day of this period few if any lever responses were recorded for each subject. This was regarded as reserpine "control" behaviour and Figures 17 and 18 show its development and final form for rats 3 and 5.

The antagonistic effects of methylphenidate were very clearly illustrated on the cumulative record. Figures 19,20 show the effects of 2.5 mg. per Kg. of methylphenidate on the reserpine "control" behaviour pattern. Shortly after injection, lever responding was re-established at a low but accelerating rate. A fairly steady rate of responding

appeared, there being little apparent difference between response rate during the interval component and that during the ratio component. Post-reinforcement pausing appeared briefly, but remained abbreviated compared to the original non-drug control data. The period of re-establishment of responding on the lever lasted approximately an hour after which there was a rapid decline in responding until the reserpine "control" baseline was reinstated.

Following the injection of 5 mg. per Kg. of methylphenidate, much the same features were noted as was the case with the preceding dosage (Figures 19,20). However, not only were the effects more pronounced and prolonged, but in addition, characteristic behavioural features of methylphenidate appeared after the behavioural effects of reserpine had been abolished. These are expressed in terms of an elevated response rate during the interval component and a depression of the same during the ratio component.

When a dosage of 10 mg. per Kg. of methylphenidate was administered, the effects noted under the 5 mg. per Kg. dosage were even more prominent (Figures 19,20). Immediately following injection, the record shows that the subjects remained unresponsive to the lever. However, the drinkometer sensing head indicated that this was a period of hyperactivity as opposed to the almost

complete absence of any motor activity under reserpine alone.

Thus, each dosage of methylphenidate used in the present study supressed the behavioural effects of reserpine and, for a period following injection, resulted in the emergence of behaviour patterns similar to those seen when methylphenidate alone, was administered.

Cumulative records provide an excellent means of identifying general trends in the results, however, for more detailed information, the three behavioural measures of response rate per minute, time required to complete the ratio run, and post-reinforcement pausing, were of greater importance.

In Figure 21, mean response rates per minute under all drug treatments are plotted in terms of percentage deviations from the control mean. Each of the mean response rate values was tested for significant deviation from the control value. For this purpose, a variation of the t-test designed to test for the significance of the difference between two means for correlated samples was employed since all the data of this study were obtained by repeated testing of the same four subjects.

It should be emphasized at this stage that results obtained from studies in the operant area are not, as a general rule,

amenable to statistical manipulation. Any procedure that seeks to identify overall trends by averaging the data from all subjects tends to obscure individual results, which are of importance in operant work when a small number of subjects is used.

Thus, the application of the t-test to the response rate per minute data yields the result that only two of the drug dosages cause a significant deviation from the control mean; 10 mg. per Kg. of pentobarbital, ($t=3.80$, $P \leq .05$), and 2.5 mg. per Kg. of methylphenidate,($t=4.58$, $P \leq .05$). Of course, response rate per minute is not a very sensitive measure, since even under control conditions there were wide individual differences, and also considerable fluctuations within the same subject.

Figure 22 shows the mean time taken to complete the requirements of the ratio components of the schedule under all drug conditions and again, is reported in terms of percentage deviations from the control mean. By means of the t-test, four of the drug treatments were shown to cause significant deviation from the control behavioural pattern. Pentobarbital at the 5 and 10 mg. per Kg. dosages, ($t=5.82$, $P \leq .05$)($t=3.58$, $P \leq .05$) respectively, methylphenidate at the 10 mg. per Kg. dosage ($t=4.09$, $P \leq .05$), and the drug combination of methylphenidate 2.5, and pentobarbital 10 mg. per Kg. ($t=12.95$, $P \leq .01$), all

resulted in a significant increase in the time taken to complete the ratio requirement.

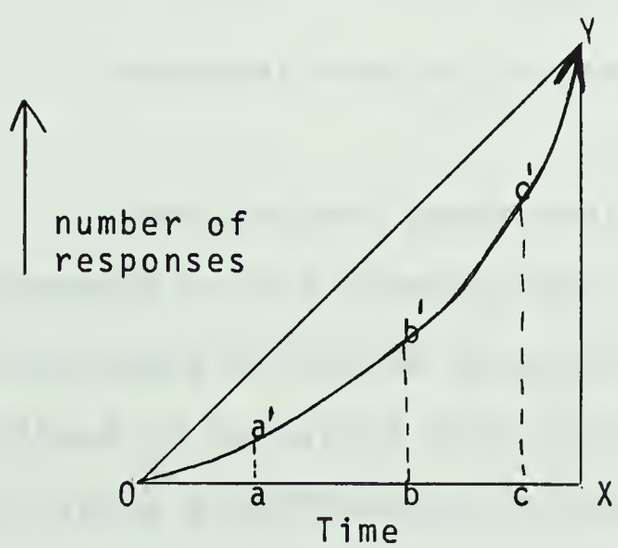
The third behavioural measure, post-reinforcement pausing was analysed, and is reported in the same manner as the two preceding measures (Figure 23) and yielded four significant values. Pentobarbital at a dosage level of 0.5 mg. per Kg. ($t=5.19$, $P \leq .05$), resulted in a significant increase in pausing, while methylphenidate at 5 and 10 mg. per Kg. ($t=3.73$, $P \leq .05$)($t=15.83$, $P \leq .01$) respectively, and the combined dosage of methylphenidate 10 mg. per Kg. and pentobarbital 2.5 mg. per Kg. ($t=5.06$, $P \leq .05$) all caused a significant decrease in post-reinforcement pausing.

The significant results reported above, are in agreement with the trends noted in the cumulative records, however, the latter show evidence of important behavioural modifications under several of the drug conditions which rated insignificant when examined by statistical techniques involving group averaged data.

The results obtained from calculation of the indices of curvature warrant particular attention in this section, since by use of this technique of data analysis, it is possible to determine general trends and detailed effects from examination of individual performance.

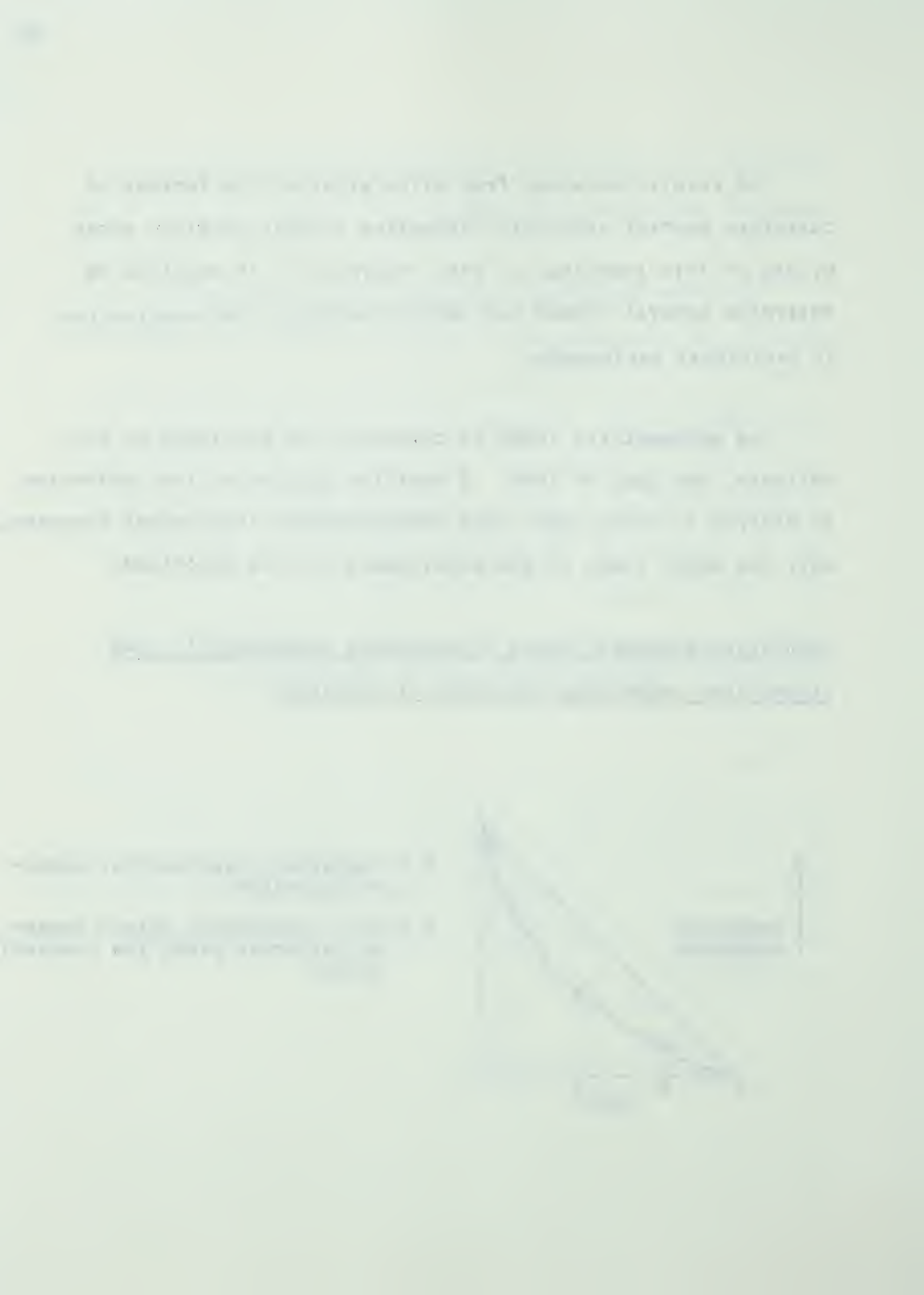
The mathematical index of curvature was developed by Fry, Kelleher, and Cook in 1960. A detailed account of the derivation is offered in their paper (see references); for the present purposes, only the major steps of the development will be described.

Cumulative-response record illustrating geometrically, the assumptions underlying the index of curvature.



O Y represents hypothetical number of responses.

O a'b'c'Y represents actual number of responses along the cumulative curve.



By calculating the areas under the curve O a a', a a'b'b etc., it is possible to obtain the number of responses occurring in each of these segments of the cumulative curve, and further, to show that a a' equals responses in the first time interval (R_1), b b' responses in the first two time intervals (R_2). c c' responses in the first three time intervals (R_3) and XY, total number of responses (R_4).

Then, the index of curvature $I = \frac{3R_4 - 2(R_1 + R_2 + R_3)}{4R_4}$

i.e., a ratio of actual number to hypothetical number of responses.

This may be expressed in a general formula for dividing the total fixed interval into any number of sub-divisions(n) as follows:-

$$I = \frac{(n-1)\,R_{n-2}\,(R_{n-1} + R_{n-2} + \ldots + R_1)}{n\,R_n}$$

A constant rate of response gives I = 0.

In the present experiment, data obtained from each interval component of the schedule was presented by the print-out counter in the form of twelve successive, twenty-second sub-divisions. Indices of curvature were calculated for two of the four subjects. Following stabilization on the schedule, all rats showed constant behaviour patterns under control conditions and the drug-induced changes in behaviour were relatively invariant. However, as already stated, there were wide individual differences in

performance; thus, rats 1 and 4 were selected for the present analysis since the former showed a consistently higher rate of responding and shorter post-reinforcement pausing than all other subjects while the reverse was true of the latter. The index was calculated for one control session, one session at each drug dosage level, one session at each combination of Pentobarbital and Methlyphenidate, one reserpine control session, and one session at each combination of reserpine and methlyphenidate. Each value reported was calculated from the data of the first ten reinforcements following the drug injection. In some cases, less than ten reinforcements followed the drug injection in which case the index was calculated from the available data.

Figure 24 shows the results obtained from the data provided by rat 1. The control value is shown at top left together with a representative portion of the cumulative record covering a single, inter-reinforcement interval. The index value of +.46 confirms that there was positive acceleration of response rate over each interval component throughout the experimental session.

The remaining segments in the top row of this figure show the effects of the four dosages of methylphenidate, in increasing order, on the interval component of the schedule.

The indices values become progressively smaller as dosage increases thus demonstrating that with increasing dosage levels, the characteristic interval behaviour patterns gradually diminish until at the 10 mg. per Kg. dosage the index approximates that of a constant rate of responding (+.03). The results, particularly those of the 5 mg. per Kg. and 10 mg. per Kg. dosages, confirm previous findings that methylphenidate, like d-amphetamine, tends to enhance low rates of responding (early part of the interval component) and depress high rates of responding (ratio component).[1]

The centre row of diagrams illustrate the effects of the four dosage levels of pentobarbital. It appears that even at the lowest dosage. Verhave's claim that interval behaviour is more sensitive to the influence of barbiturates than is ratio behaviour is substantiated. The index value under .5 mg. per Kg. is higher than that under control conditions, which indicates that the interval curvature is enhanced. This is confirmed both by the segment shown in figure 24 and by the cumulative records of rats 3 and 5 under the same drug levels. The same trend may be observed in the following two segments representing 2.5 and 5 mg. per Kg. of pentobarbital respectively. As far as the 10 mg. per Kg.

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1. Data from ratio behaviour does not, of course, form any part of the calculation of the index, however, inspection of the segments of cumulative records reproduced in this figure, especially the 2.5, 5, and 10 mg. per Kg. dosage levels, substantiate this point.

dosage is concerned, it should be borne in mind that this resulted in virtual anaesthetization of the subject for the greater part of the experimental session. The index value was calculated from data obtained towards the end of the session when the subject had, again started to respond. Its high value which indicates a recovery of interval behaviour may be attributed in part to another of Verhave's findings; namely the excitatory effect of pentobarbital when its influence is diminishing.

The segments in the lower part of the figure are concerned with data obtained from the interactive effects of pentobarbital and methylphenidate in five dosage combinations.

In all cases except one, the index value fell between the extremes represented by the drugs acting individually. The exception is that obtained from the interactive effects of 2.5 mg. per Kg. of methylphenidate and 10 mg. per Kg. of pentobarbital. The index in this case is identical with that from 10 mg. per Kg. pentobarbital acting alone. The implications of these results are dealt with in more detail in the discussion section.

Figure(25) presents similar data obtained from rat 4. The same trends are evident here that appeared in the data obtained from rat 1, and as in the latter case, are discussed more fully in the following section.

Finally in this section, the individual results obtained from rats 1 and 4 under reserpine and methylphenidate are presented in figure 26. From the cumulative records presented in figures 19 and 20 it is evident that chronic administration reduces the response rate to zero. These records were obtained from subjects 3 and 5, but the same was also true for rat 1 and 4. The indices of curvature in figure 26 illustrate the antagonistic effect of methyphenidate on the effects of reserpine. At a 2.5 mg. per Kg. dosage of methylphenidate the subject started to respond and behaviour characteristic of the interval component was somewhat restored. This trend was more pronounced at the 5 mg. per Kg. dosage, and, in the case of rat 4, the index value was restored almost to the control level. A decline in the index value was apparent at the 10 mg. per Kg. dosage of methyphenidate which indicates that the effect of the latter was not only to abolish the behavioural effects of reserpine but also to superimpose an effect similar to that observed when methylphenidate alone is administered. As in the case of the preceding data reported here, the implications of these results will be more fully discussed in the following section.

DISCUSSION

Prior to an examination of the drug-induced behavioural modifications observed in this study, it is important to establish the assumption that the schedule of reinforcement employed induced patterns of behaviour characteristics of those observed under both ratio and interval schedules acting independently. Confirmatory evidence is provided by the control cumulative record (Figure 1). Clearly, a post-reinforcement pause is followed by a period during which the response rate is relatively low but shows an accelerative trend such that the subject is responding at a high rate when it enters the ratio component. This high rate is maintained throughout the ratio component and is characteristic of behaviour generated by a ratio schedule operating independently. Further substantiating evidence is provided by the indices of curvature obtained from the data of a control session (Figures 24,25). The values of +.46 and +.36 confirm that the behaviour pattern of the subjects during the interval component of the schedule was characteristic of that generated by fixed interval schedules alone. The result is in accordance with those previously reported by Ferster and Skinner following their detailed examination of Tandem schedules of reinforcement.

It is appropriate, at this point, to preface the discussion of the effects of pentobarbital with a reference to a general

finding of other workers in this field.

Dews, (1958) and Kelleher et. al. (1961), have presented convincing evidence in support of the claim (by Dews) that in the case of amphetamines, drug effect is dependent upon the response rate engendered by the schedule employed. Waller and Morse (1963) suggest that similar dependencies exist in the case of barbiturates, but whereas amphetamines tend to increase a low response rate and decrease a high response rate, the reverse appears to be the case when barbiturates are administered.

The results that emerged following administration of pentobarbital show unequivocally that the drug has differential effects on the two components[1] of the schedule. Perhaps the most important feature of the action of this drug is expressed in terms of post-reinforcement pausing and time taken to complete the ratio requirement.

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1. It should be pointed out that the characteristic pattern of responding generated by a FI schedule is a low but accelerating rate which culminates in a high response rate shortly before a reinforcement is obtained. Thus in a Tandem FI FR schedule, the high terminal response rate of the FI component merges inperceptibly with the high rate typically engendered by the FR component. Thus when behavioural changes occurring in the FI requirement are referred to, it is the initial low rate that is of primary interest. A similar restriction applies to the ratio requirement where the latter part is of importance. However, for convenience, the terms "interval component" and "ratio component" are retained.

The lower dosages (i.e. 0.5, 2.5 and 5 mg. per Kg.) all tended to increase the post-reinforcement pause, thus it follows that time of onset of responding during the interval component was delayed. The effect was most marked at the lowest dosage of pentobarbital (0.5 mg. per KG.) and diminished as dosage level increased. Response rate during the ratio component was also diminished by pentobarbital, but in this case the degree of depression was directly proportional to dosage. This trend is best illustrated by the 10 mg. per Kg. dosage, at which level the post-reinforcement pause was abbreviated (as compared with control data), but time taken to complete the ratio requirement was considerablly increased (Figure 8).

Dews (1955), Kelleher, et al (1961), Waller and Morse (1963) and other workers in this field have shown that small doses of pentobarbital (in the range of 1 to 3 mg. per Kg.) consistently produce decrements in responding on 5 to 15 minute FI schedules, and increase response rates on FR schedules (in the range of FR 30 to FR 50).

As will be recalled from the review of the literature, the general conclusion of the above authors was that behaviour on a fixed interval schedule (or component) is more sensitive to the effects of a barbiturate than fixed ratio behaviour. The major trends of the present study support these findings,

particularly at the 0.5 mg. per Kg. dosage level where post-reinforcement pause was extended into the interval component, while the response rate during the ratio component was unaffected. The authors mentioned above also pointed out that the dosage levels of pentobarbital that decreased response rate on interval schedules increased response rate on ratio schedules. This effect did not appear in the corresponding components of the schedule employed in the present study; Herrnstein and Morse reported a similar finding.

These results serve to emphasize the point made by Morse that environmental variables are of great importance in determining the behavioural effects of a given drug. Thus, even though the tandem schedule is composed of interval and ratio components the behavioural effects of a drug differ significantly from those seen under the same drug conditions but when the components are acting as independent schedules.

A further point that should be mentioned at this stage, is the claim made by Carlton in 1957 that the medium in which pentobarbital is dissolved prior to injection exerts a considerable influence in determining the resulting behaviour patterns. He found that administration of a water solution of the drug resulted in marked depression of response output, and that this effect was significantly attenuated when the barbiturate was in a solution of 10% ethyl alcohol, 20% propylene

glycol and 70% water, and this effect was maintained up to dosages of 10 mg. per Kg. of the drug. The latter solution was the medium employed in the present study. While Carlton recognizes that the effects of the barbiturate are contingent upon the requirements placed on the subject by the schedule of reinforcement employed, he also suggests that the alcohols serve to compensate for the barbiturate induced depression via the synaptic facilitation which they induce. Carlton employed only FI schedules in his study, and thus the schedule determinants of drug action were quite different from those pertaining in the present work. It seems reasonable to suppose that the Tandem schedule employed here, modified the effect noted by Carlton, since inspection of the appropriate cumulative records leaves no doubt that the 5 and 10 mg. per Kg. dosages of pentobarbital not only reduced response output, but caused a complete cessation of responding for a period following injection. The possibility remains, however, that the alcohol medium was instrumental in contributing to the rapid re-establishment of a high response rate and the abbreviated post-reinforcement pause during the period identified by Verhave as the post-depression excitatory phase.

The major trend emerging from the results obtained following the administration of methylphenidate, was the enhancement of response output during the interval component, and a depression

of the same during the ratio component, the effect in both cases being directly proportional to dosage level. It is apparent that while the 0.5 mg. per Kg. dosage of methylphenidate does not significantly change the post-reinforcement pausing, the remaining dosages decrease pausing so that the subject starts responding earlier in the interval component. The cumulative records (Figures 9,10 and 11) show that response rate was elevated during this component and confirmation of this point is provided by the indices of curvature. The same cumulative records, show the marked depression of response rate during the ratio component.

These findings are in accordance with those of Dews (1955) who found an increase in the pecking response of pigeons following administration of methylphenidate. They are also in agreement with the work of Dews and Morse (1961) and Mechner and Latranyi (1963). The work of Kelleher and Morse (1964) and Smith (1964) on the behavioural effects of d-amphetamine confirm that this drug influences behaviour in much the same way as does methylphenidate.

Considering the general trends emerging from the above two drugs acting independently, a further point emerges, namely that the pentobarbital induced behavioural changes appear to be the reverse of those induced by methylphenidate. This

difference is not simply in "psychomotor stimulant/psychomotor depressant" terms which, as was pointed out in the review of the literature, is now a questionable distinction, but, rather, in terms of their influence on behaviour characterized by a low response rate and that which typically shows a high rate of response. Waller and Morse (1963) demonstrated that pentobarbital tended to decrease response rate under FI schedules and increase it under FR schedules and a similar trend was evident in the present study. Precisely the reverse was true of the results obtained following methylphenidate administration. This serves to re-emphasize the fact that drug induced behavioural effects are dependent upon the nature of the ongoing behaviour, and also highlights the inadequacy of the gross classification of these drugs as psychomotor "stimulants" or "depressants".

Turning now, to the synergistic effects of methylphenidate and pentobarbital. From the above discussion of the independent effects of the drugs, and the findings of other workers in this area, it is reasonable to assume that the simultaneous behavioural effects of these drugs may be logically predicted.

At the 2.5 mg. per Kg. dosage of each drug, it would be expected from this and previous studies, that pentobarbital would depress the response rate during the interval component whereas methylphenidate would tend to cause an elevation of response output. However, there is well documented evidence

(Carlton and Didamo 1960, Carlton 1961, Weiss and Laties 1963, Smith 1964, Rutledge and Kelleher, 1964), that small dosages of pentobarbital enhance the behavioural effects of amphetamine. The action of the latter has been shown to be very similar to that of methylphenidate (Mechner and Latranyi, 1963) and thus, in the present case, simultaneous administration of 2.5 mg. per Kg. of both drugs may be expected to result in an enhancement of response rate exceeding that caused by methylphenidate alone. The relevant cumulative records (Figure 12) provide substantial evidence that this pattern was emerging in the present study. In addition, the data obtained from the post-reinforcement pausing behaviour (Figure 23) indicated a similar trend. During the ratio component, the overall effect of the two drugs was to depress slightly, the response rate, although this was not observed in all subjects. It is apparent in the record of rat 3, but rat 5 shows no deviation from control conditions (Figure 12). It is of importance to note that the control response rate for rat 3 was relatively low, while rat 5 showed a high rate of responding under control conditions. Dews (1958), Kelleher et.al. (1961), Morse (1960) and Waller and Morse (1963) working with both amphetamines and barbiturates, have all reported a similar finding; that within individual subjects, drug effect is dependent upon response rate. The present work confirms this finding with pentobarbital and methylphenidate when the drugs are acting alone and when they are administered simultaneously.

The trends noted under the above conditions also appeared, but were somewhat modified under the 5 mg. per Kg. dosages of each drug. (Figure 15).

Again, an enhancement of response rate under the interval component would be expected, and this undoubtedly appeared. However the enhancement effect was not of the same magnitude as that induced by 5 mg. per Kg. of methylphenidate alone. It will be recalled that the equivalent dosage of pentobarbital alone depressed response rate during this component, and to a greater extent than did the 2.5 mg. per Kg. dosage (index values +.57 and +.25 respectively). Thus it may be concluded that following the administration of the two drugs at the 5 mg. per Kg. level, the increased response rate effect is still operative, but is somewhat tempered by the rate depressive action of pentobarbital which is asserting itself at this level of concentration. This result also serves to emphasize the point that although two drug dosages may be equal in physical concentration, they cannot under any circumstances be regarded as equivalent in terms of their influence on behaviour.

During the ratio component there was a depression of response rate similar to, but more marked than that observed under the 2.5 mg. per Kg. dosage of each drug (Figure 15). Both drugs acting independently at this dosage level, tended to enhance response rate, and it would seem reasonable to conclude that

when injected simultaneously, the rate depressive tendencies (at low dosages) of methylphenidate with respect to this schedule component is potentiated by the pentobarbital. This may be clarified by drawing attention to the similar effects obtained when methylphenidate was administered alone, at this and the two lower dosages.

The effects of the 10 mg. per Kg. dosage of each drug require little comment beyond the statement that the trend observed at the 5 mg. per Kg. level was continued in exaggerated form at this dosage level, and precisely the same relationships obtained. (Figure 16).

The remaining drug combinations investigated during this phase of the study were 10 mg. per Kg. methylphenidate with 2.5 mg. per Kg. pentobarbital and 10 mg. per Kg. of the latter with 2.5 mg. per Kg. of the former. From Figure 13 it is evident that the first of these dosage combinations caused a significant reduction in post-reinforcement pausing and an associated elevation of response rate during the interval component (index value +.11); the reverse was true of the second dosage pair (Figure 14). It is evident that in the first case, the pentobarbital is exerting a modifying influence over the extreme effects of the high methylphenidate dosage while in the second case, the tendency of the high pentobarbital

dosage to induce an overall depression of the response rate (general anaesthetic property) has been reduced by the opposite tendency in the methylphenidate dosage to produce a result similar to that observed when 5 mg. per Kg. of pentobarbital is acting alone.

As far as the ratio component is concerned, similar modifications occurred with the result that the 2.5 mg. per Kg. dosage of pentobarbital clearly inhibits the rate-diminishing effect of the high methylphenidate dosage. With the second of the two drug combinations, the overall rate-depressive effect of the high pentobarbital dosage is modified by the 2.5 mg. per Kg. methylphenidate dosage. The resulting reduction in time taken to complete the ratio requirement (Figure 14) cannot be attributed solely to the methylphenidate which when acting alone, tends to depress response rate during the ratio component, but rather to a potentiation of possible rate-enhancement effects of pentobarbital which are normally masked at high levels by its anaesthetic properties.

Considering now, the general conclusions that may be drawn from the preceding discussion. Evidence has been presented in support of the claim that pentobarbital in small dosages slightly decreases response rate during the interval component. However, very small dosage differences appear to be a critical factor since the 0.5, 2.5 and 5 mg. per Kg.

dosages decrease response rate while the 10 mg. per Kg. dosage increases this rate. It has also been shown that the same drug does not affect response rate significantly during the ratio component at the two lower dosages, but at the 5 and 10mg per Kg. level, response rate is considerably decreased. Methylphenidate was shown to have properties very similar to those previously reported for amphetamine; an enhancement of response rate in the interval component, and a depression, at the two lower dosages, of the ratio component response rate. The 5 and 10 mg. per Kg. dosages increase ratio response rate, this being attributable to the overall excitant properties of the drug at this level.

As far as the effects of the simultaneous administration of the drugs are concerned, whether the drugs compliment or antagonise each other appears to depend on both the concentrations of the drugs relative to each other, and the schedule component under consideration. In addition, when the highest dosage of either drug is involved, it tends to mask any synergistic or antagonistic relationships between the drugs. There is evidence that following the 2.5 mg. per Kg. dosage of each drug, an overall enhancement of responding during both the interval and ratio components resulted. This general trend was identified in the results obtained from other dosage combinations, but in some cases the drug behaviour relationship was more complex and therefore each combination of the drugs was dealt with independently.

Previous studies in the field of drug interaction have been primarily concerned with amphetamines and barbiturates, but more important, the schedules employed have, in general, engendered relatively low rates of responding. This led Steinberg et. al. (1961) and Rushton et.al. (1963) to suggest that low levels of motor activity are caused by fear and anxiety associated with introduction to a novel environment and that amphetamine/barbiturate combinations might have increased activity by alleviating these sources of stress. This viewpoint is untenable when the results of Weiss and Laties (1964) and Rutledge and Kelleher (1964) are considered (see Review of Literature). In addition, since methylphenidate has been shown to act in a fashion similar to that of amphetamine, the results of the present study also fail to support the above suggestion, since the schedule employed generated high rates of responding both in the latter part of the interval component, and throughout the ratio component. Thus, both high and low rates of responding can, under appropriate conditions, be enhanced by the two drugs acting simultaneously.

Finally in this section, the effects of methylphenidate and reserpine acting simultaneously are examined in more detail.

During the establishment of reserpine "control" behaviour (Figures 17,18) it is apparent that the behaviour characteristic of the interval component disappears at a comparatively early

stage while responding during the ratio component persists for a much longer period. This is a further illustration of the dependency of drug effect upon established patterns, of responding.

As the effects of the chronic reserpine treatments developed, ratio responding was also disrupted, but in a manner quite different from that induced by high dosages of barbiturates. The latter results in a gradual diminishing and final cessation of responding whereas reserpine induces long pauses that are interspersed throughout the ratio run. This was clearly shown in the cumulative records obtained from rat 5 (Figure 20) and is quite atypical of the normal pattern of ratio responding. These results are in complete accordance with those of Dews (1956). The appearance of this phenomenon was followed, within a few sessions, by complete cessation of responding (Figures 17, 18), at which stage, methylphenidate was administered in a series of dosages.

In all cases, methylphenidate restored responding behaviour, and the degree of restoration was proportional to the dosage administered. That this was a true reversal of the reserpine effects is illustrated by the fact that the 2.5 mg. per Kg. dosage of methylphenidate produced little recovery of the behaviour characteristic of the interval component, and restored ratio behaviour in two of the subjects, to the point where

prolonged pauses were interspersed between periods of rapid responding (Figures 19,20).

However, again this effect is dependent upon whether the individual subject characteristically responds at a relatively high or low rate under non-drug, control conditions i.e., the effect is apparent in rat 4 which characteristically responded at a relatively low rate, but not in rat 1 where the original control response rate was high. In the latter case, a greater degree of restoration of responding was apparent.

The same general trend appeared at both the 5 and 10 mg. per Kg. dosages of methylphenidate. In Figure 26 the interval response rate of rat 4 is restored almost to the non drug control level (index values +.34 and +.36 respectively). However, in rat 1, the characteristic effect of methylphenidate, namely increased responding during the interval component, is re-established. Moreover, in rat 4, the ratio component response rate is depressed; again a characteristic feature of the influence of methylphenidate. For rat 1, this dosage results in the appearance of the overall excitatory effect of methylphenidate and the response rate is elevated in both components. These trends appear in exaggerated form following administration of 10 mg. per Kg. of methylphenidate.

A further point which must be considered at this stage is that made by Sidman (1956). Investigating the effects of reserpine on avoidance behaviour, he found that low dosages of the drug tended to enhance response rate. He also noted a similar effect with subjects performing on a D.R.L. schedule (differential reinforcement of low response rates), and it is recognized that while direct evidence is lacking, this may be an influential factor in the present study.

Thus, it would appear that the reserpine/methylphenidate interaction requires the consideration of several factors in order that it may be adequately characterized:-

1. Chronic reserpine treatment results in a cessation of responding which is restored by methylphenidate.

2. The degree of restoration is directly proportional to the methylphenidate dosage value.

3. The degree of restoration is also dependent upon the rate of responding characteristic of the individual subject under non drug control conditions, i.e., where this response rate is relatively high, recovery of responding is accelerated.

4. Reserpine may itself enhance response rate, thus adding to the methylphenidate effect, but this in turn is dependent upon the non-drug control response rate of the individual concerned.

5. As is the case with other drugs generally classified as psychomotor depressants, the different behaviour patterns engendered by the two components of the schedule of reinforcement determine the manner in which the effects of reserpine are expressed and these are quite distinct from each other.

In conclusion it may be stated that the data presented in this study serve to emphasize the interdependence of pharmacological and behavioural variables. It is clear that as Sidman (1958) stated "the relations between drugs and behaviour are a function not only of the drug but also of the conditions under which the behaviour is generated". The remaining important point to be made is that the present study lies within the framework of behavioural pharmacology which is concerned with the effects of drugs on the behaviour of the intact animal. There are obvious close relationships between this and other pharmacological sub-disciplines such as neuropharmacology which is concerned with effects of drugs on nervous tissue. While recognizing the close connections and anticipating a closer rapproachment

between these fields, it must be emphasized that until more detailed information is available in both areas, the specification of the aims and goals of each will continue to be a useful distinction.

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A P P E N D I C E S

FIGURE 5

The final 25 sessions of the period during which the subjects were stabilized on the Tandem FI4 FR 30 schedule. The last 6 sessions during which the performance of each subject satisfied the stability criterion (see text) are marked by open circles.

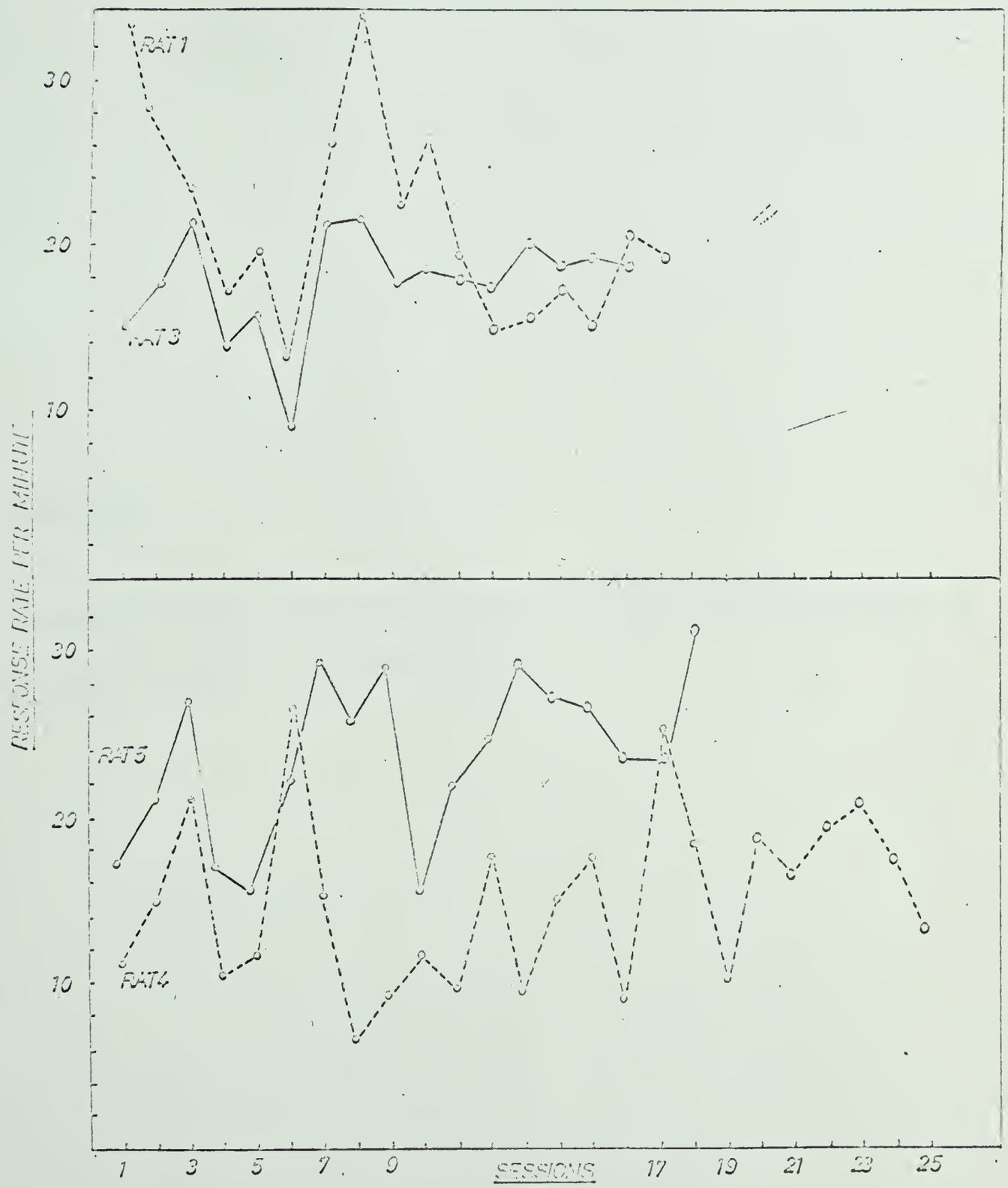
RAT 1
RAT 3
RAT 5
RAT 4
30
20
10
RESPONSE RATE PER MINUTE
1
3
5
7
9
SESSIONS
17
19
21
23
25

FIGURE 6

Cumulative records obtained following the administration of 2.5 mg. per Kg. of pentobarbital.

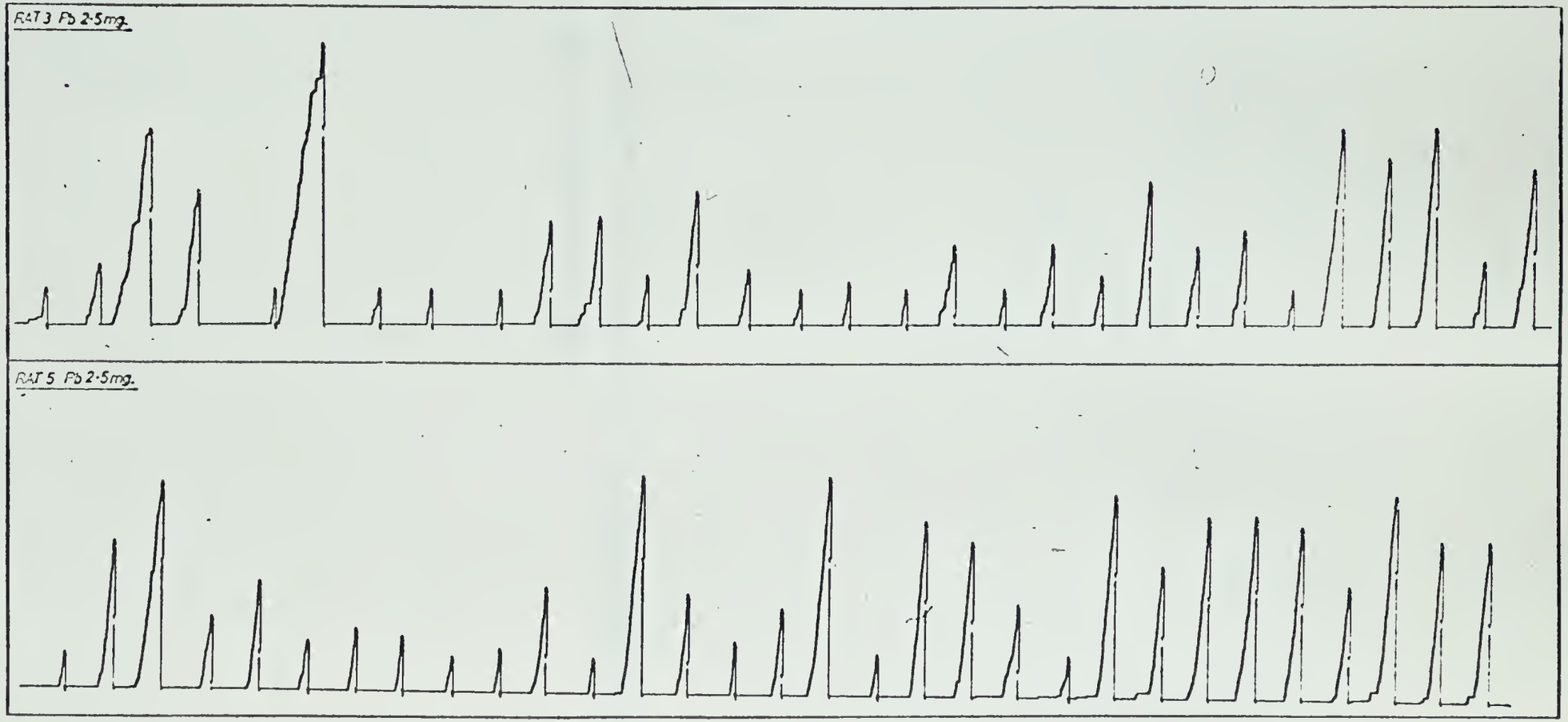
RAT 3 Pb 2·5mg.
RAT 5 Pb 2·5mg.

FIGURE 7

Cumulative records obtained following the administration of 5 mg. per Kg. of pentobarbital.

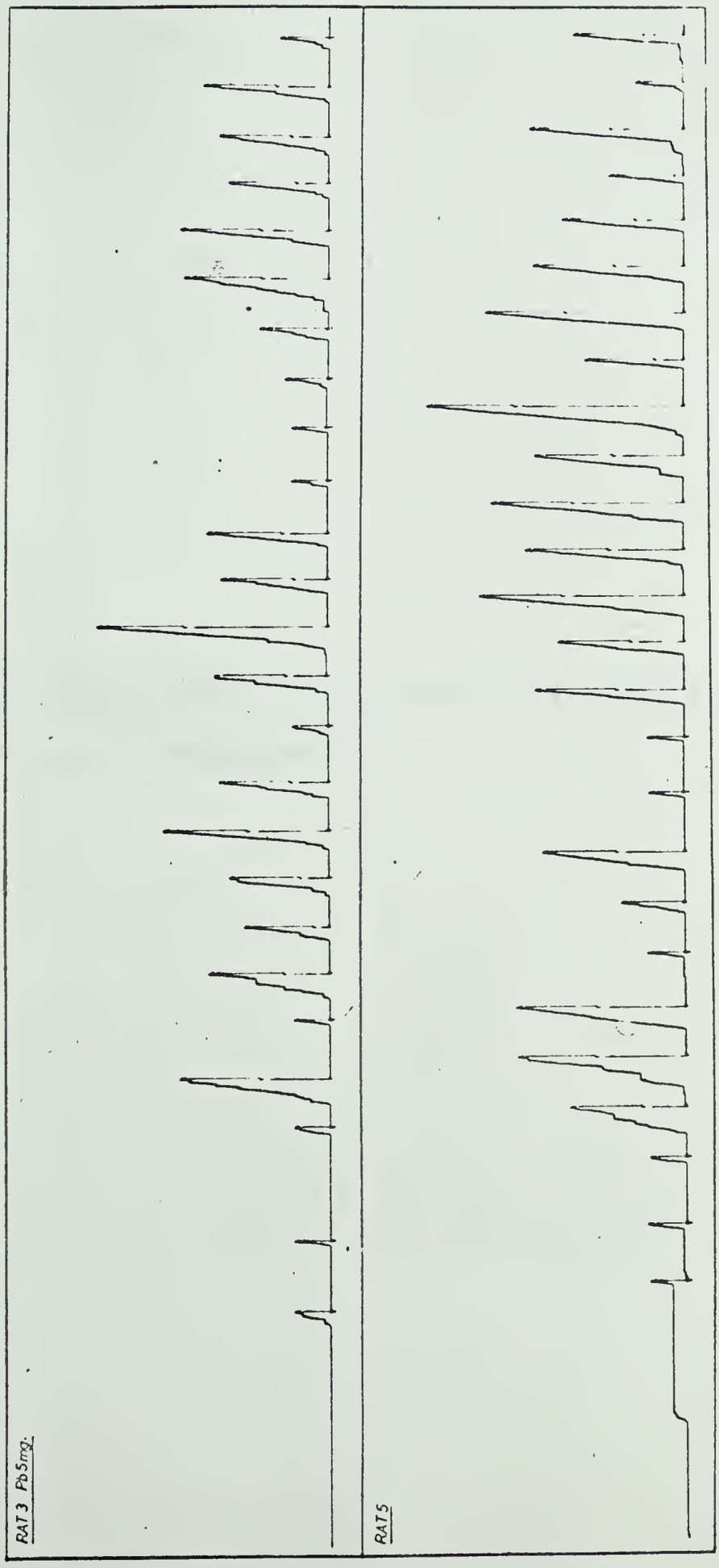
RAT 3 Pb 5mg.
RAT 5

FIGURE 8

Cumulative records obtained following the administration of 10 mg. per Kg. of pentobarbital.

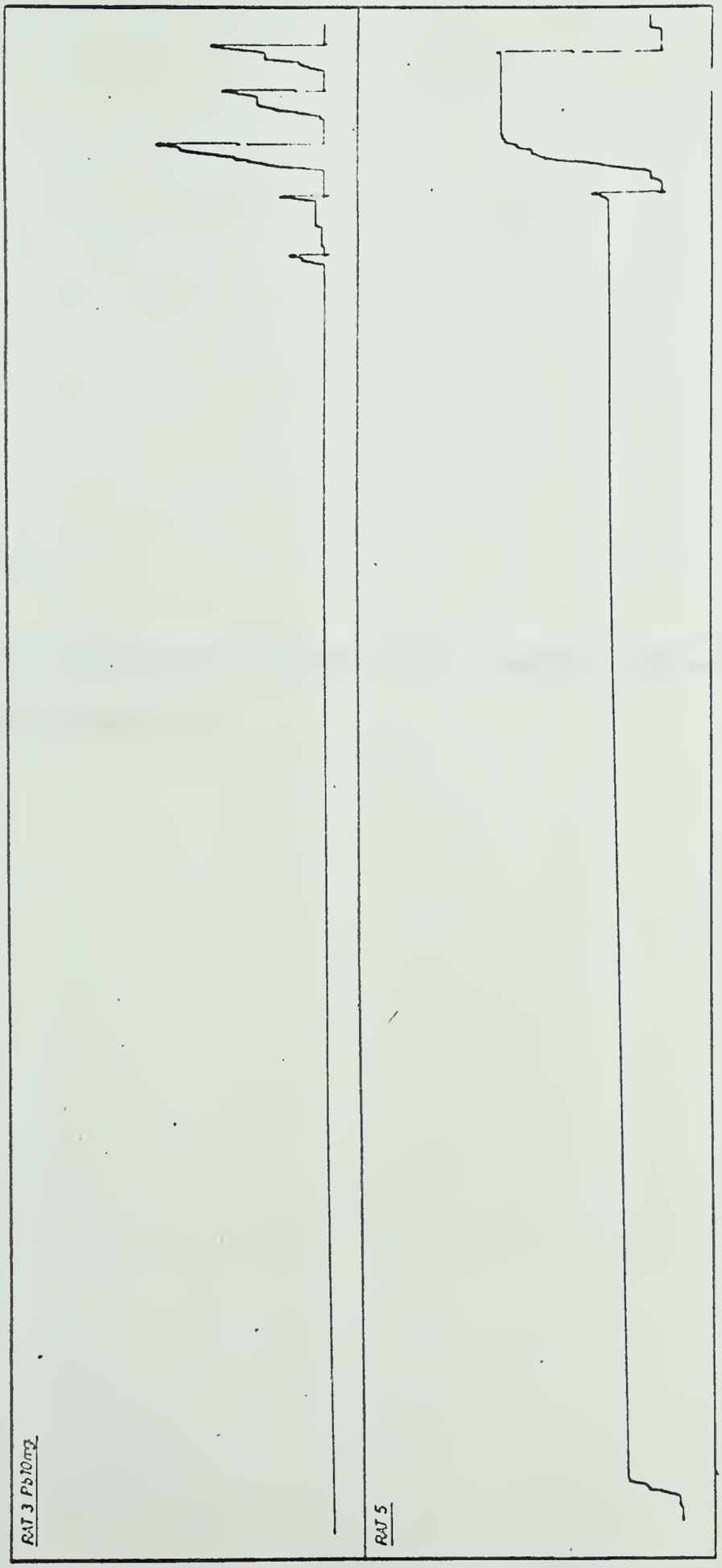
RAT 3 Ps10mg
RAT 5

FIGURE 9

Cumulative records following the administration of 2.5 mg. per Kg. of methylphenidate.

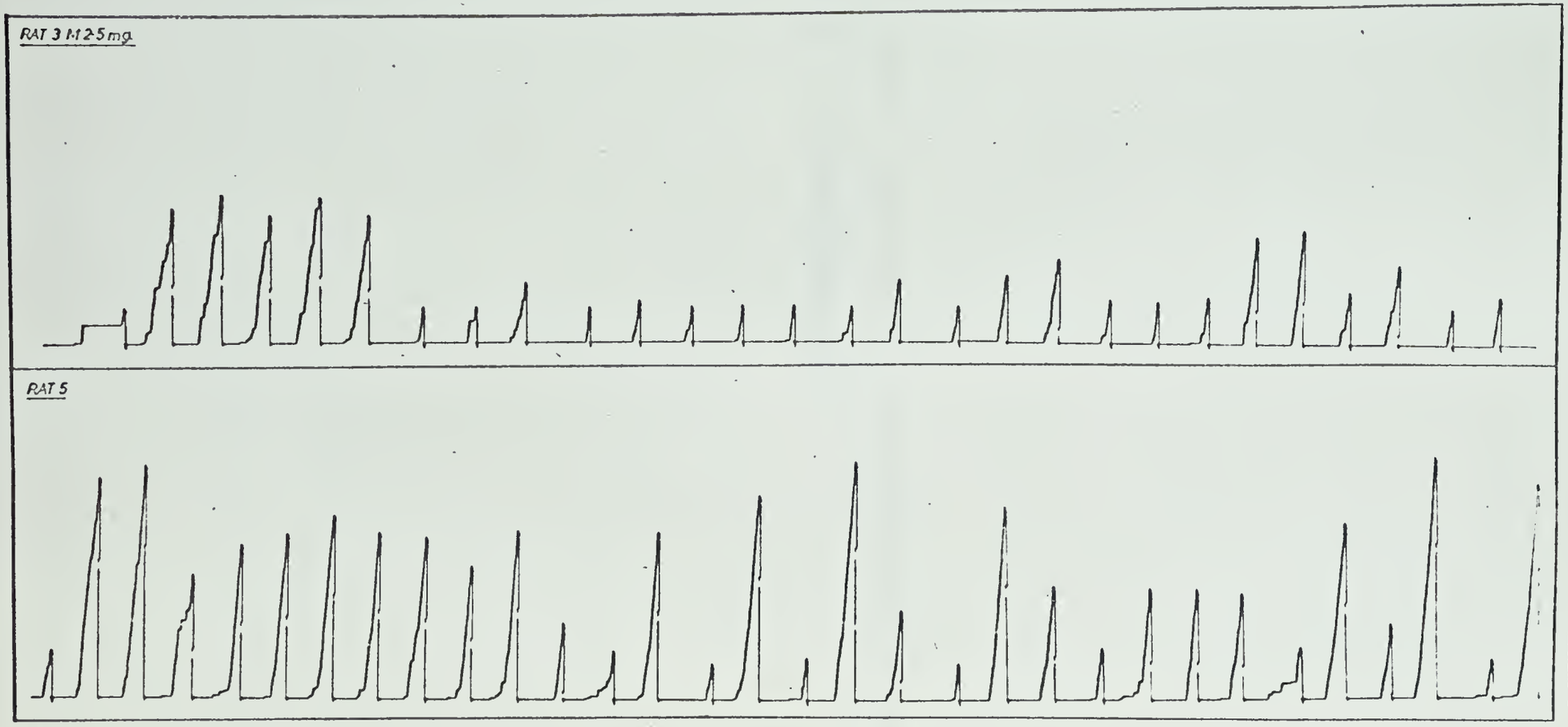
RAT 3 M 12·5 mg.
RAT 5

FIGURE 10

Cumulative records obtained following the administration of 5 mg. per Kg. of methylphenidate.

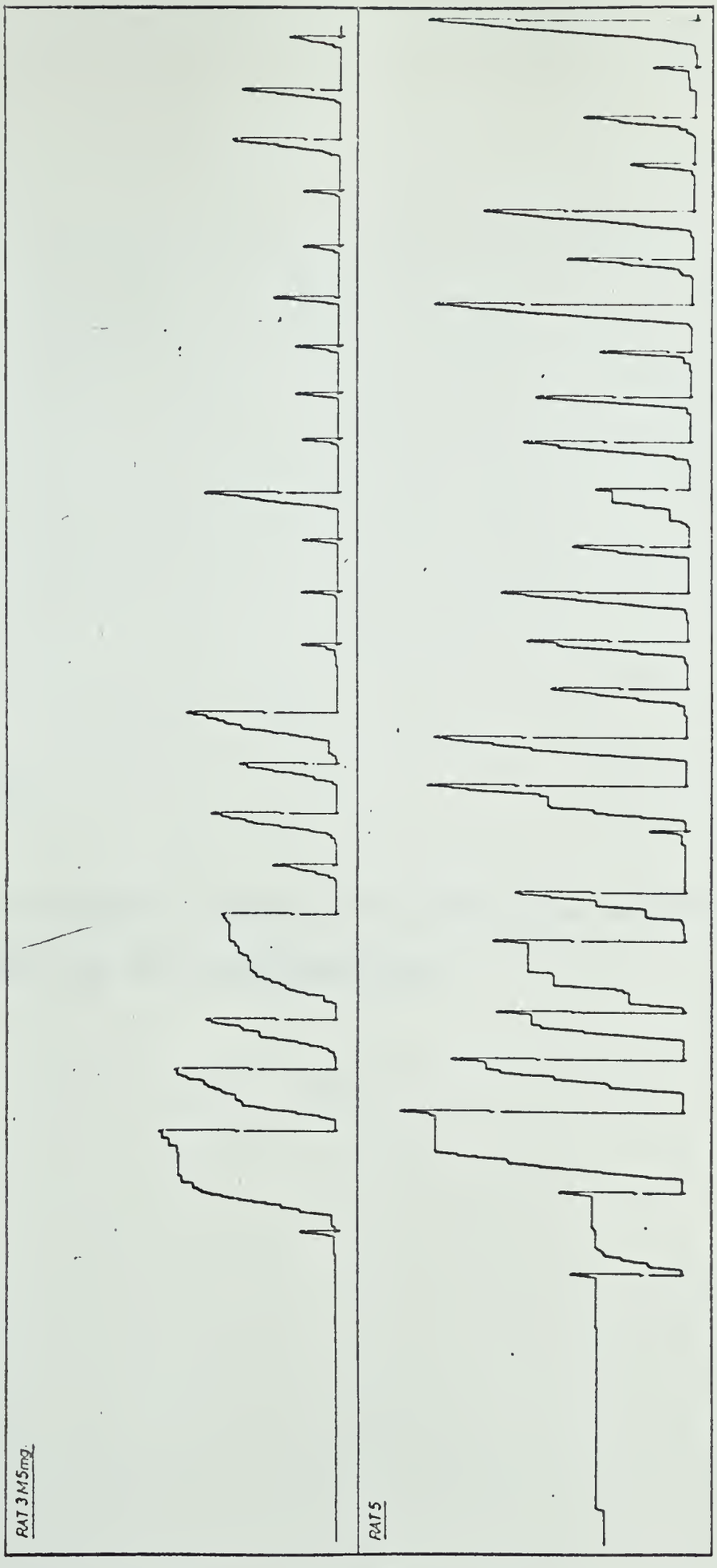
RAT 3 MSmg.
RAT 5

FIGURE 11

Cumulative records obtained following the administration of 10 mg. per Kg. of methylphenidate.

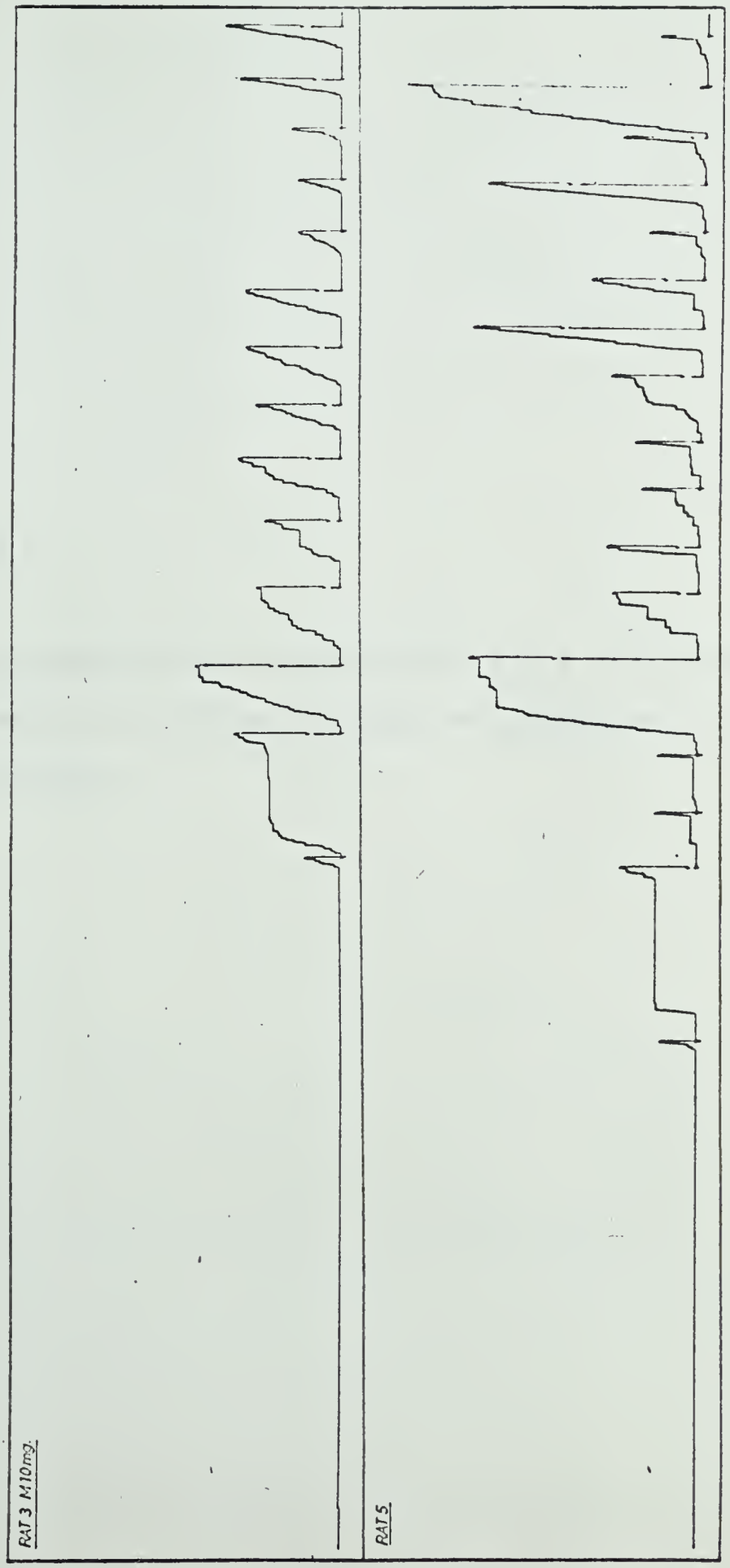
RAT 3 M10mg.
RAT 5

FIGURE 12

Cumulative records obtained following the simultaneous administration of 2.5 mg. per Kg. of pentobarbital and methylphenidate.

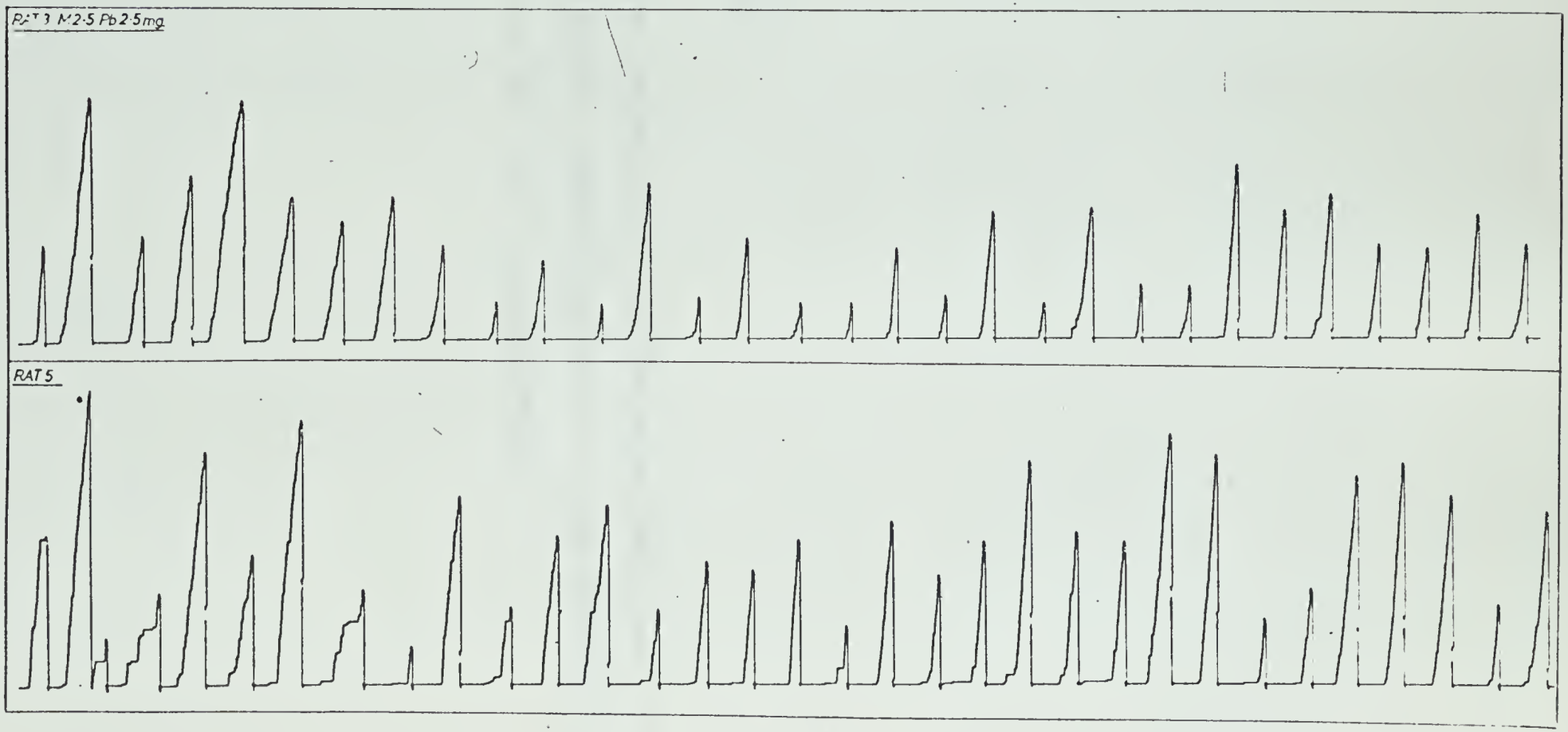
RAT 3 M 2·5 Pb 2·5 mg
RAT 5

FIGURE 13

Cumulative records showing the behavioural modifications induced by simultaneous administration of 10 mg. per Kg. of methylphenidate and 2.5 mg. per Kg. of pentobarbital.

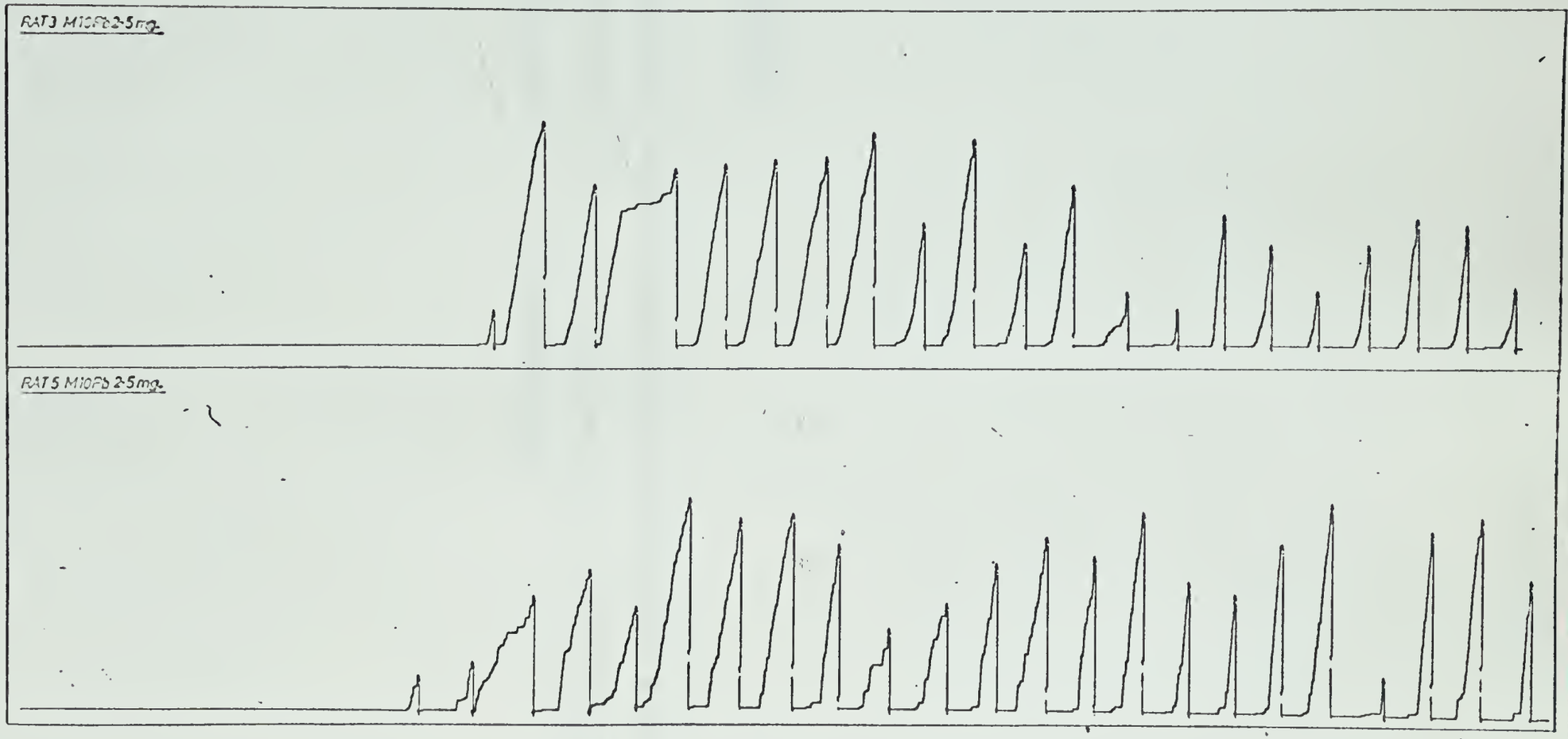
RAT 3 M10Pb 2·5mg.
RAT 5 M10Pb 2·5mg.

FIGURE 14

Cumulative records obtained following the simultaneous administration of 2.5 mg. per Kg. of methylphenidate and 10 mg. per Kg. of pentobarbital.

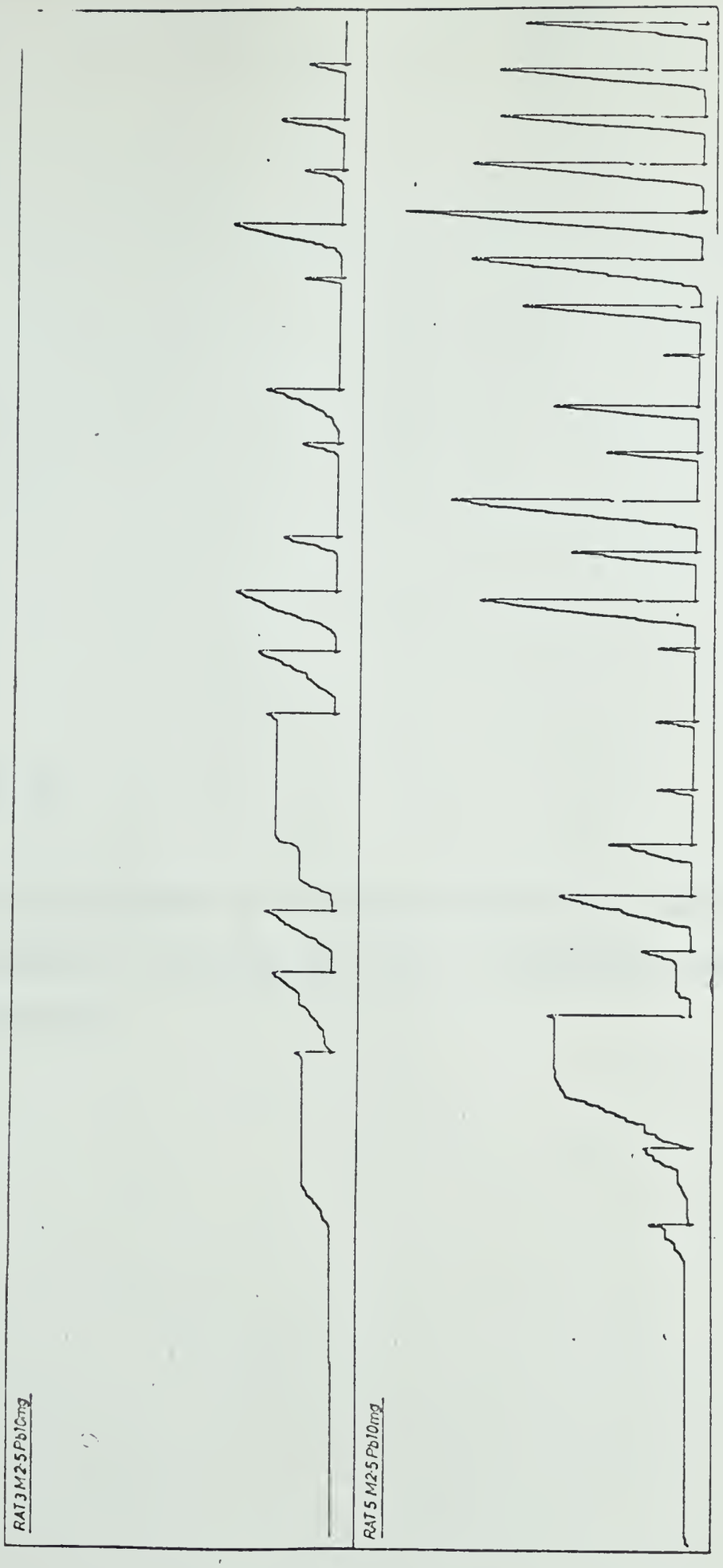
RAT 3 M 2-5 Pb 10mg
RAT 5 M 2-5 Pb 10mg

FIGURE 15

Cumulative records obtained following the simultaneous administration of 5 mg. per Kg. of methylphenidate and pentobarbital.

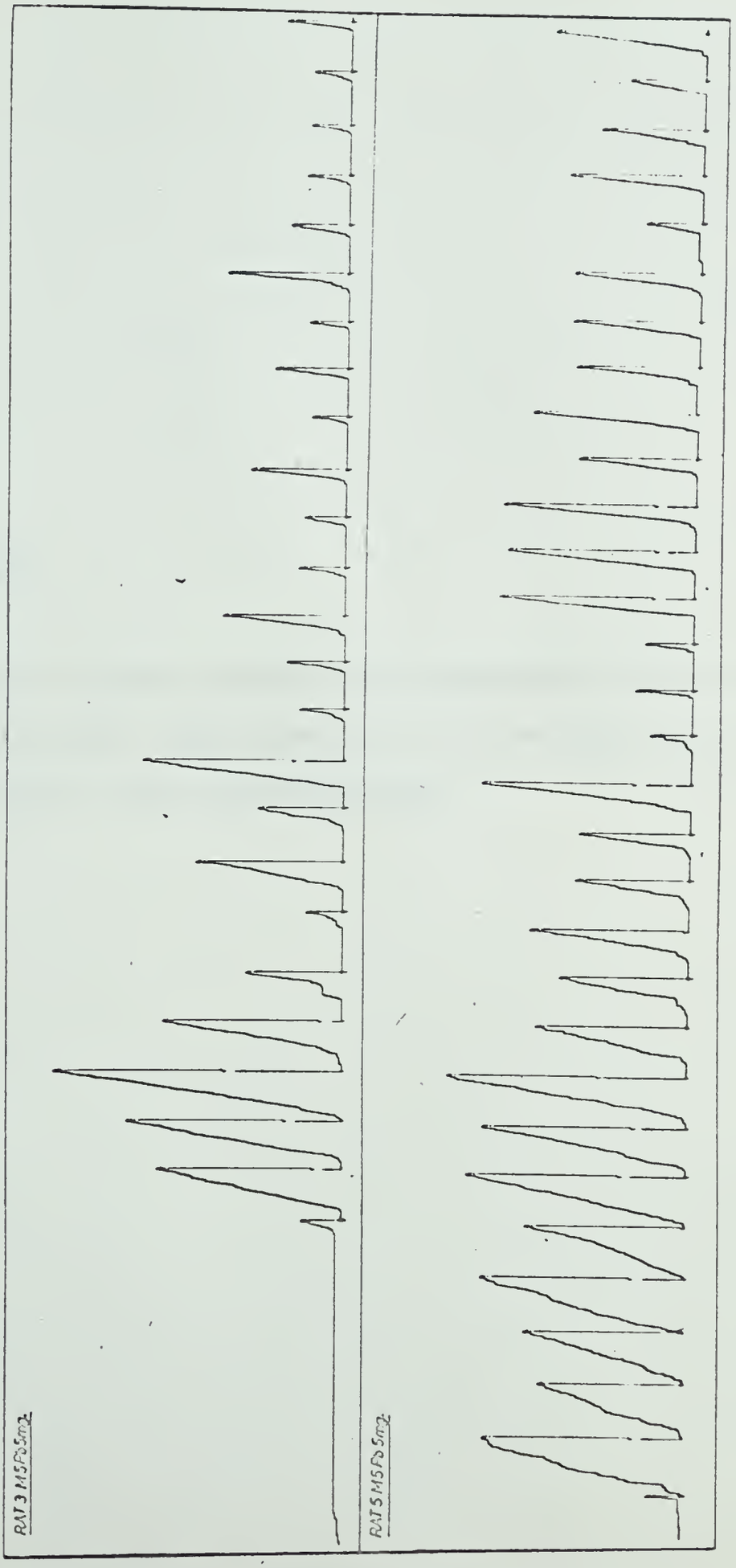
RAT 3 MSPD 5mg2
RAT 5 MSPD 5mg2

FIGURE 16

Cumulative records showing the behavioural modifications induced by simultaneous administration of 10 mg. per Kg. of both pentobarbital and methylphenidate.

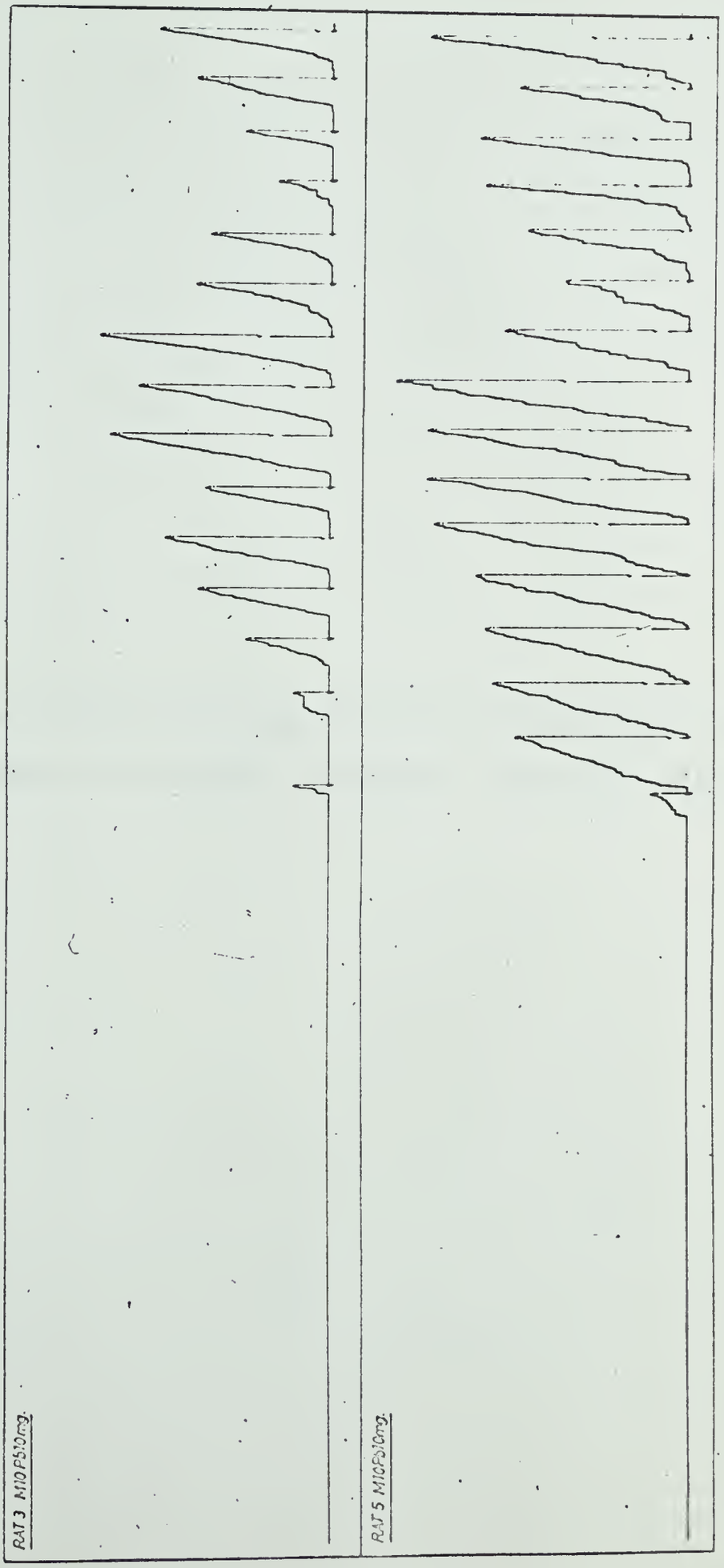
RAT 3 M10PS10mg.
RAT 5 M10PS10mg.

FIGURE 17

Cumulative records obtained from Rat 3 during the period of establishment of reserpine "control" behaviour (see text).

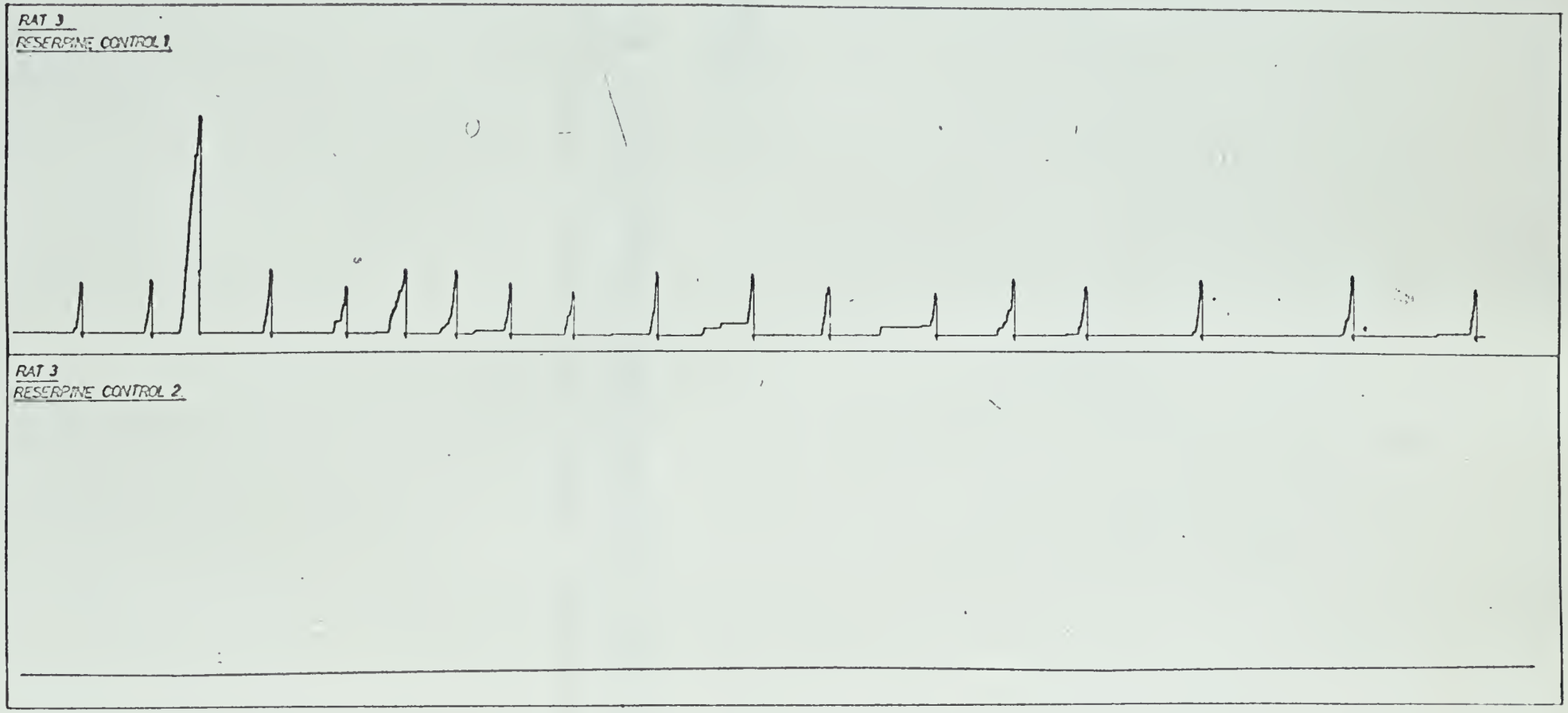
RAT 3
RESERPINE CONTROL 1
RAT 3
RESERPINE CONTROL 2

FIGURE 18

Samples of cumulative records obtained from Rat 5 during the establishment of reserpine "control" conditions (see text).

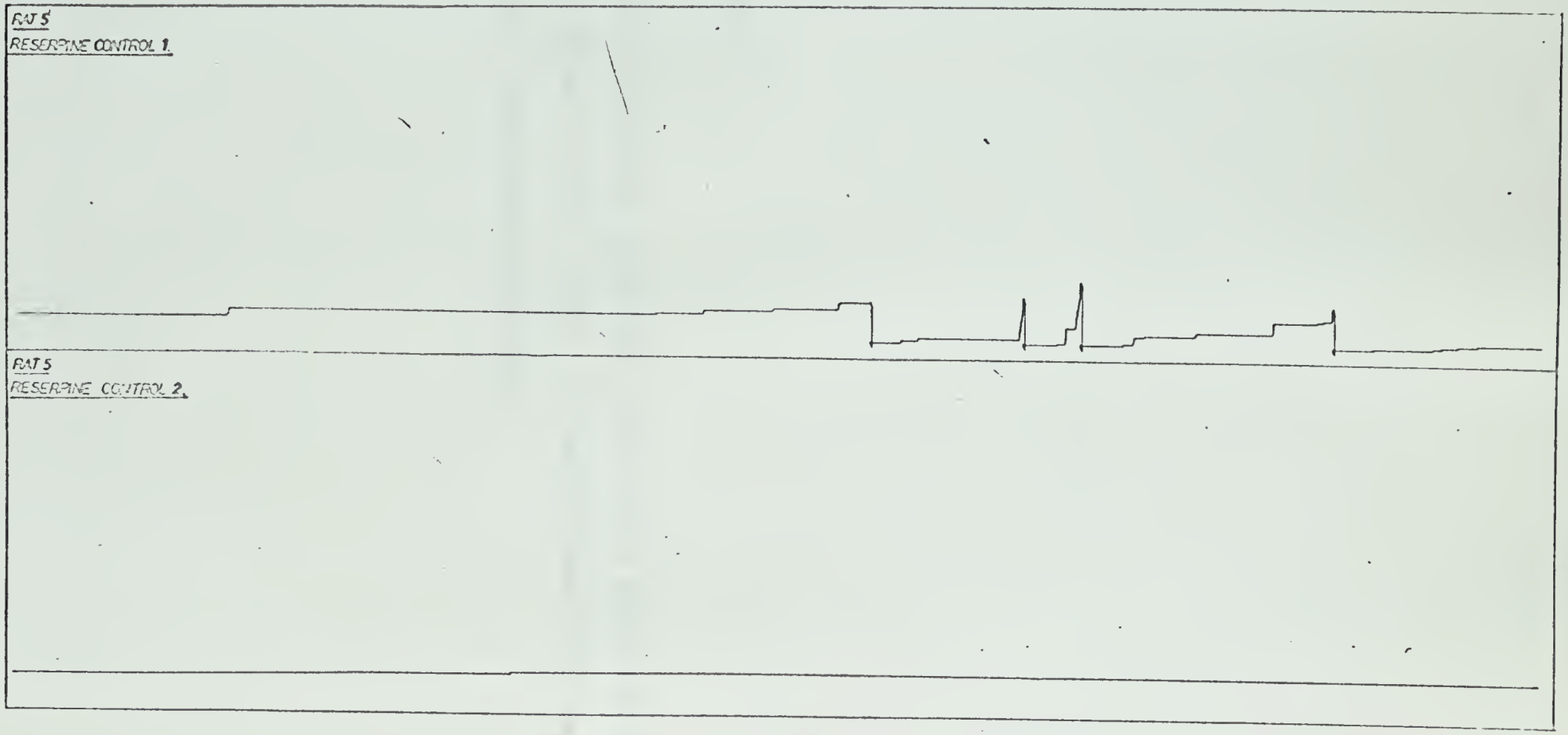
RAT 5
RESERPINE CONTROL 1.
RAT 5
RESERPINE CONTROL 2.

FIGURE 19

Cumulative records obtained from Rat 3 showing the influence of the three dosage levels of methylphenidate on the reserpine "control" behaviour patterns.

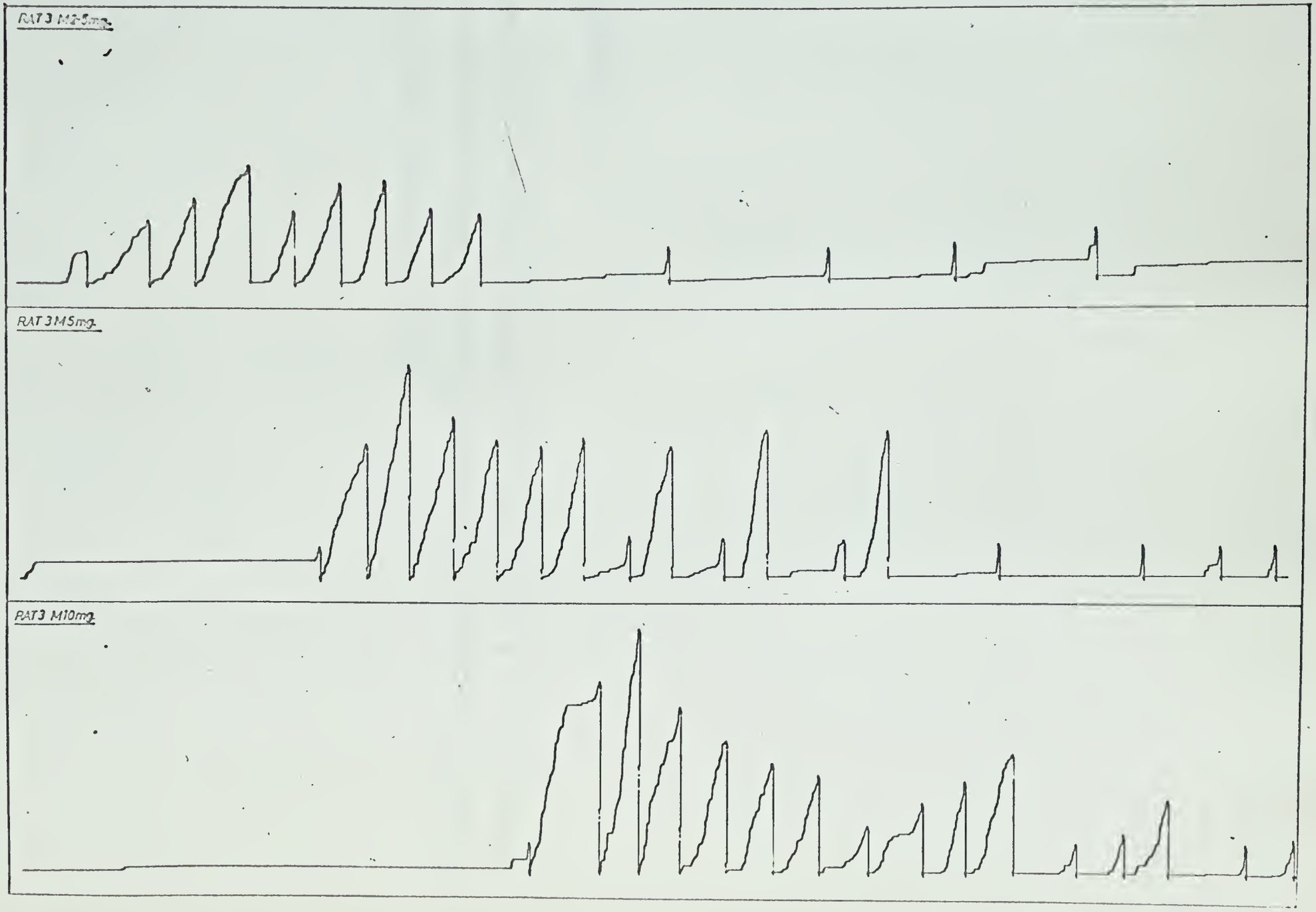
RAT 3 M2·5mg.
RAT 3 M5mg.
RAT 3 M10mg.

FIGURE 20

Cumulative records obtained from Rat 5 showing the influence of the three dosage levels of methylphenidate on the reserpine "control" behaviour patterns.

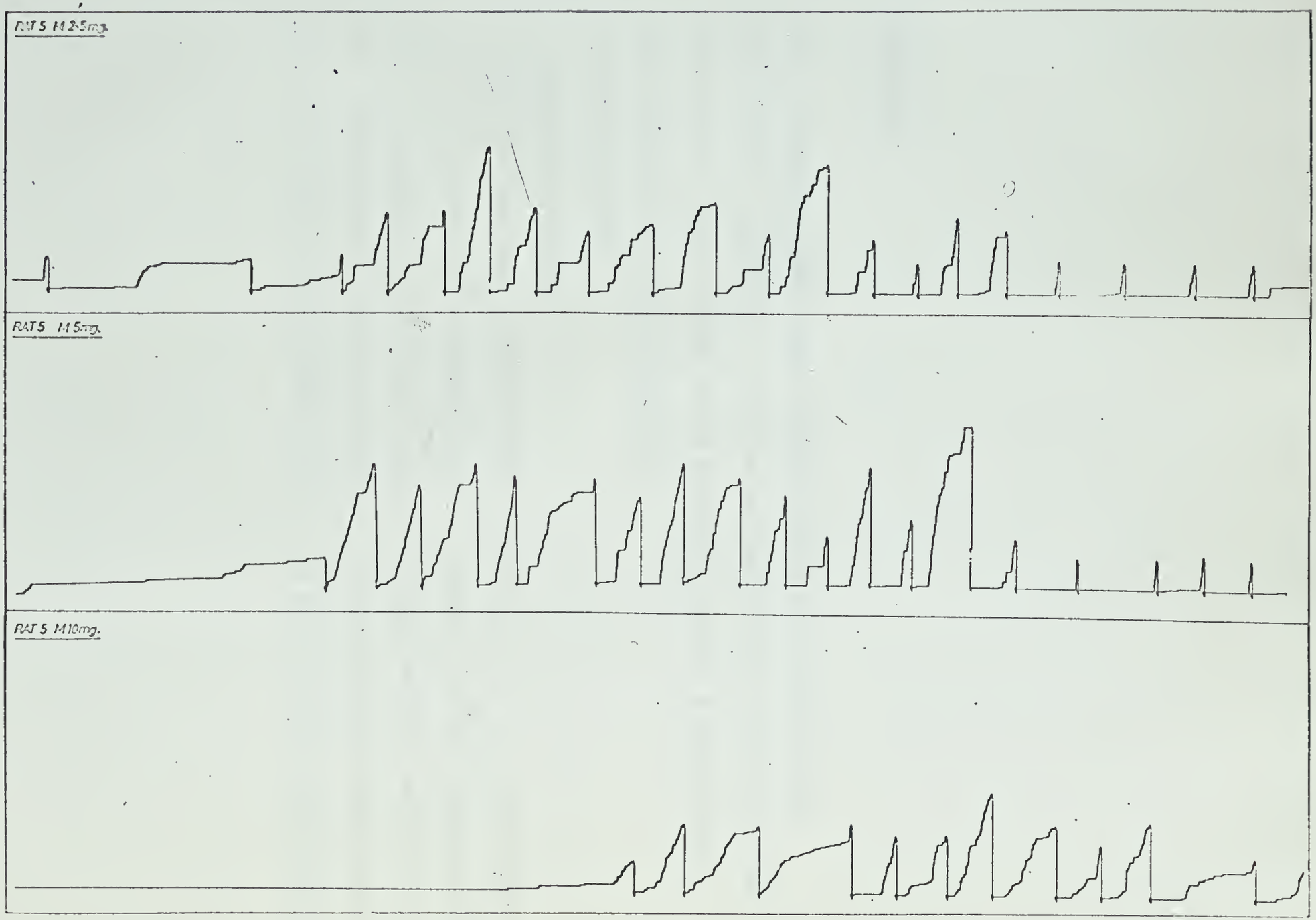
RAT 5 M 2.5mg.
RAT 5 M 5mg.
RAT 5 M 10mg.

FIGURE 21

This histogram shows mean response rate per minute under experimental conditions in terms of percentage deviation from the control value. Each value was obtained by averaging the data obtained from all subjects.

Pb= Pentobarbital

M = Methylphenidate

a = 2.5 mg. per Kg. pentobarbital + 2.5 mg. per Kg. methylphenidate

b = 2.5 mg. per Kg. pentobarbital + 10 mg. per Kg. methylphenidate

c = 10 mg. per Kg. pentobarbital + 2.5 mg. per Kg. methylphenidate

d = 5 mg. per Kg. pentobarbital + 5 mg. per Kg. methylphenidate

e = 10 mg. per Kg. pentobarbital + 10 mg. per Kg. methylphenidate

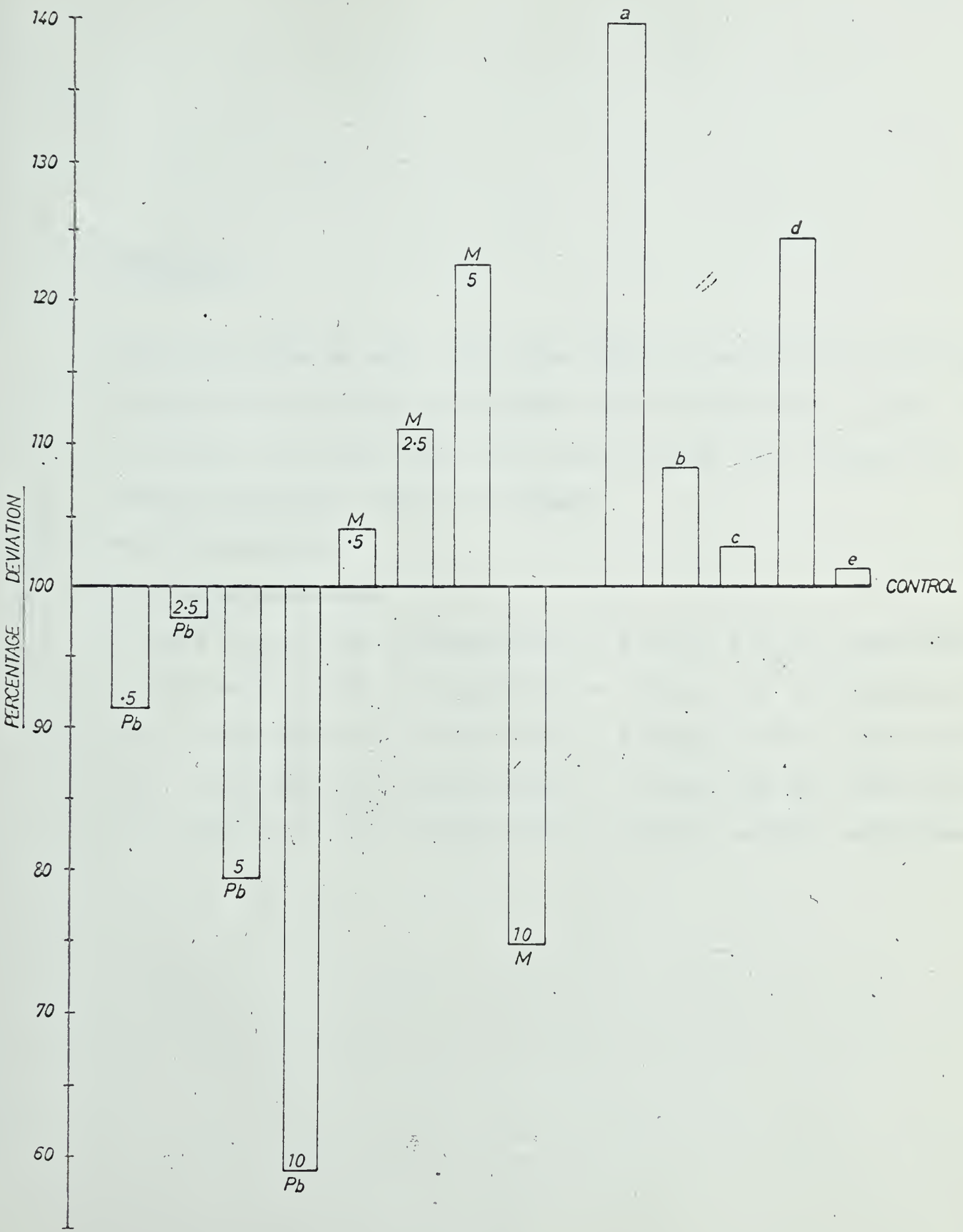
140
130
120
110
100
90
80
70
60
PERCENTAGE DEVIATION
a
b
c
d
e
CONTROL
M
·5
M
2·5
M
5
·5
Pb
2·5
Pb
5
Pb
10
Pb
10
M

FIGURE 22

Histogram showing mean time taken under experimental conditions, to complete the ratio requirement and is expressed in terms of percentage deviation from the control value. All values are averages obtained from all subjects.

Pb= Pentobarbital

M = Methylphenidate

a = 2.5 mg. per Kg. pentobarbital + 2.5 mg. per Kg. methylphenidate

b = 2.5 mg. per Kg. pentobarbital + 10 mg. per Kg. methylphenidate

c = 10 mg. per Kg. pentobarbital + 2.5 mg. per Kg. methylphenidate

d = 5 mg. per Kg. pentobarbital + 5 mg. per Kg. methylphenidate

e = 10 mg. per Kg. pentobarbital + 10 mg. per Kg. methylphenidate

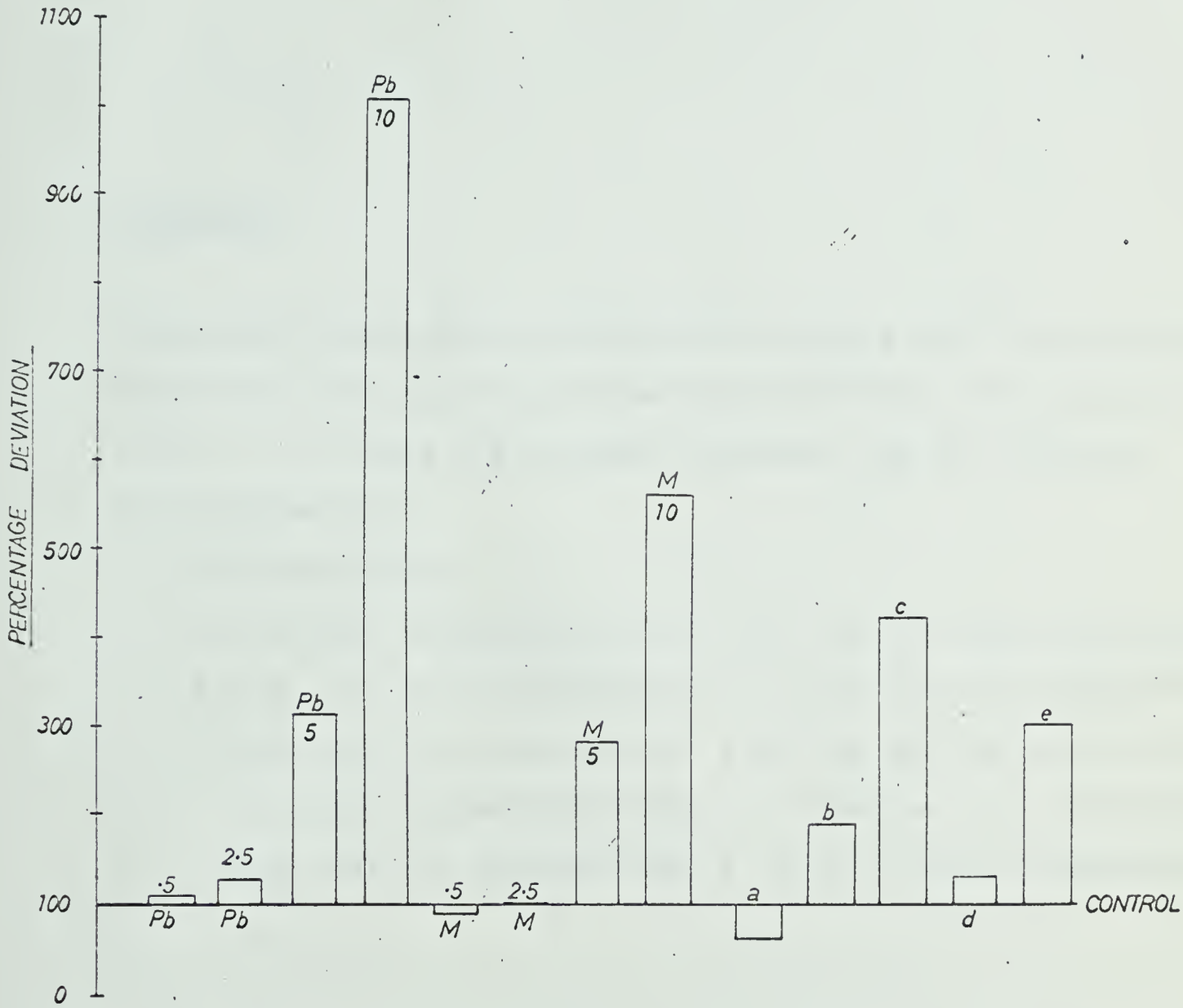
1100
900
700
500
300
100
0
PERCENTAGE DEVIATION
Pb 10
Pb 5
2·5 Pb
·5 Pb
·5 M
2·5 M
M 5
M 10
a
b
c
d
e
CONTROL

FIGURE 23

Histogram showing post-reinforcement pausing under experimental conditions, expressed as percentage deviations from the control value. All values are averages obtained from all subjects.

Pb= Pentobarbital

M = Methylphenidate

a = 2.5 mg. per Kg. pentobarbital + 2.5 mg. per Kg. methylphenidate

b = 2.5 mg. per Kg. pentobarbital + 10 mg. per Kg. methylphenidate

c = 10 mg. per Kg. pentobarbital + 2.5 mg. per Kg. methylphenidate

d = 5 mg. per Kg. pentobarbital + 5 mg. per Kg. methylphenidate

e = 10 mg. per Kg. pentobarbital + 10 mg. per Kg. methylphenidate

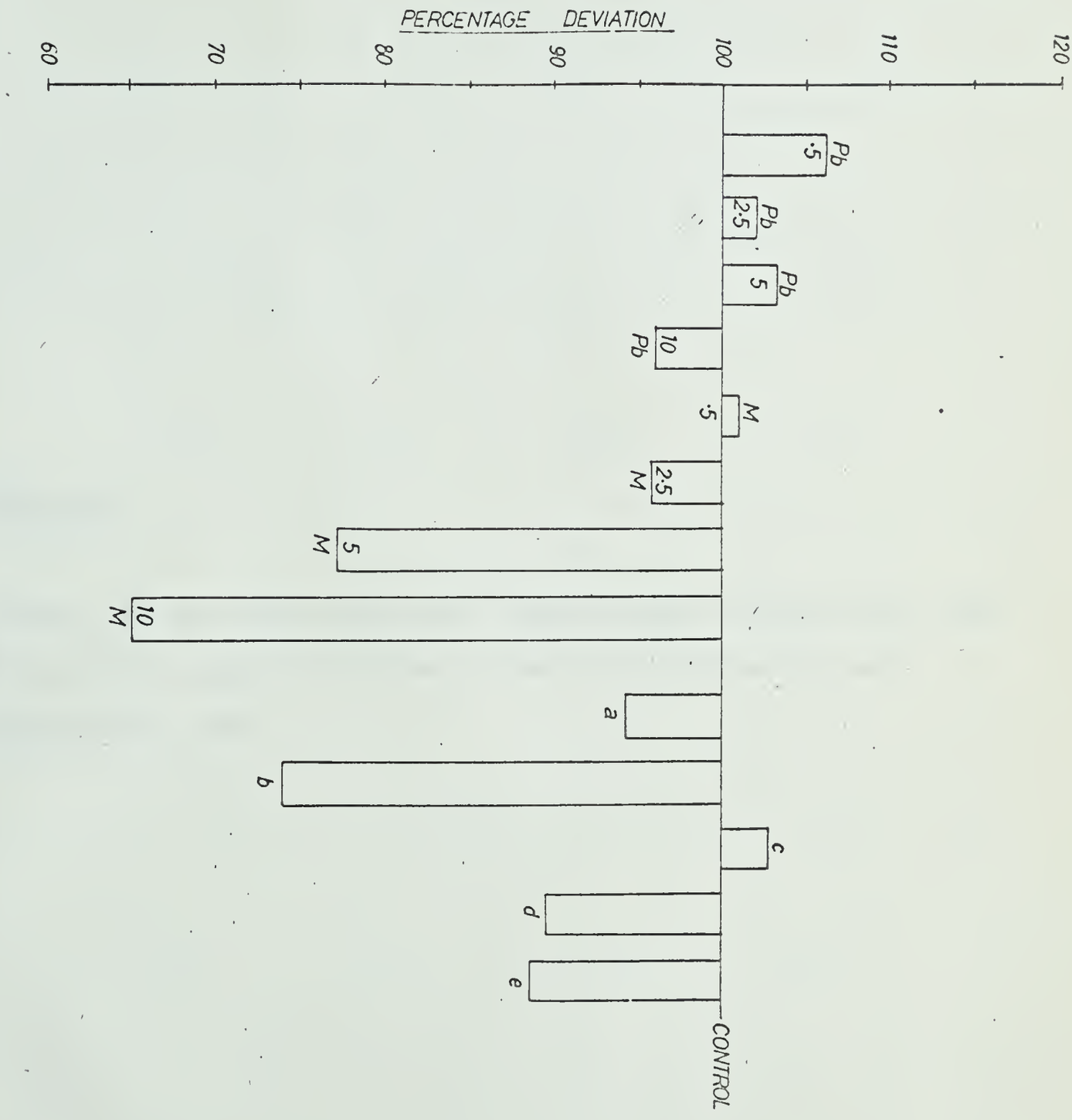
PERCENTAGE DEVIATION
60
70
80
90
100
110
120
Pb .5
Pb 2.5
Pb 5
10 Pb
M .5
2.5 M
5 M
10 M
a
b
c
d
e
CONTROL

FIGURE 24

Indices of curvature for Rat 1 under control conditions, and following the administration of methylphenidate (M) and pentobarbital (Pb).

RAT 1

± ·46 	± ·44 	± ·16 	± ·06 	± ·03 
CONTROL	M·5mg.	M 2·5mg.	M 5mg.	M 10mg.
RATE COORDINATES 	± ·59 	± ·49 	± ·32 	± ·42 
	Pb·5mg.	Pb 2·5mg.	Pb 5mg.	Pb 10mg.
± ·33 	± ·31 	± ·22 	± ·42 	± ·25 
M 2·5 + Pb 2·5mg.	M 5 + Pb 5mg.	M 10 + Pb 2·5mg.	M 2·5 + Pb 10mg.	M 10 + Pb 10mg.

FIGURE 25

Indices of curvature for Rat 4 under control conditions and following the administration of methylphenidate (M) and pentobarbital (Pb).

RAT 4

+·35	+·54	+·47	-·12	-·12
CONTROL	M·5mg.	M 2·5mg.	M 5mg.	M 10mg.
RATE COORDINATES (100 responses, 1, ·5, ·25, 5 minutes)	+·52	+·25	+·57	+·22
	Pb·5mg.	Pb 2·5mg.	Pb 5mg.	Pb 10mg.
+·40	+·05	+·11	+·22	+·67
M 2·5 + Pb 2·5mg.	M 5 + Pb 5mg.	M 10 + Pb 2·5mg.	M 2·5 + Pb 10mg.	M 10 + Pb 10mg

FIGURE 26

Indices of curvature for Rats 1 and 4 obtained following the administration of methylphenidate while the subjects were under reserpine "control" conditions (see text).

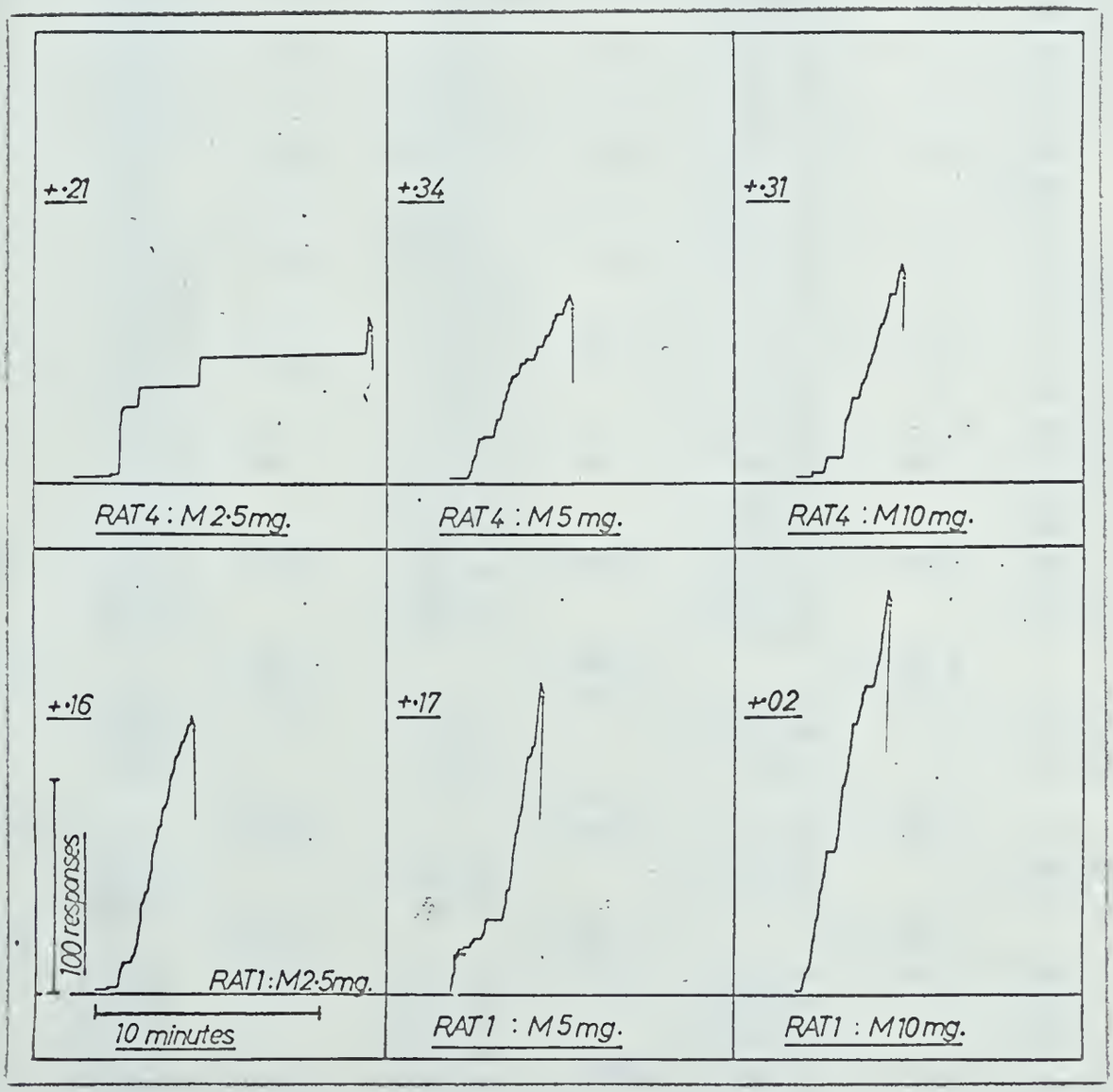
+·21
+·34
+·31
RAT 4 : M 2·5 mg.
RAT 4 : M 5 mg.
RAT 4 : M 10 mg.
+·16
+·17
+·02
100 responses
RAT 1 : M 2·5 mg.
10 minutes
RAT 1 : M 5 mg.
RAT 1 : M 10 mg.

TABLE 1. RATIO TIME (in .5 sec intervals)

RAT I		RAT III		RAT IV		RAT V		MEAN	
C1	72.96	C1	438.68	C1	76.0	C1	39.35	C	69.76
2	78.48	2	180.1	2	59.46	2	51.13	P.5	72.92
3	53.20	3	43.56	3	75.55	3	37.23	P2.5	84.71
4	57.46	4	44.32	4	56.92	4	37.16	P5	245.37
5	41.86	5	51.78	5	60.93	5	40.76	P10	1530.8
6	59.33	6	36.40	6	79.93	6	28.29	M.5	62.43
7	69.53	7	52.56	7	56.79	7	35.45	M2.5	69.84
8	62.50	8	54.90	8	142.04	8	40.51	M5	103.86
9	62,00	9	55.80	9	84.76	9	33.86	M10	396.80
10	104.48	10	56.06	10	44.33	10	34.30	M2.5	
C.M.=	66.18	C.M.=	101.42	C.M.=	73.67	C.M.=	37.80	P2.5	51.77
P.5	47.63	P.5	101.28	P.5	131.24	P.5	35.90	M10	
	62.60		168.64		79.34		42.77	P2.5	129.36
	42.03		60.65		70.13		32.8	M2.5	
P_2.5	125.10	P2.5	120.57	P2.5	95.67	P2.5	37.96	P10	600.06
	56.43		97.48		100.64		73.00	M5P5	96.64
	57.13		64.51		153.56		34.41	M10	
P5	433.7	P5	333.3	P5	228.78	P5	203.75	P10	209.79
	183.76		418.61		187.75		105.41		
	390.12		161.65		160.73		136.96		
P10	957.8	P10	1763.0	P10	507.62	P10	2541		
	159		0.0		644.15		1299		
	0.0		3368.0		2622.0		4508		
M.5	65.93	M.5	56.43	M.5	47.38	M.5	51.86		
	71.51		37.58		171.76		49.33		
	47.83		55.55		58.63		35.46		
M_2.5	54.20	M2.5	73.42	M2.5	61.65	M2.5	53.72		
	64.31		85.71		67.03		40.70		
	74.89		79.57		122.92		60.07		
M5	69.00	M5	115.11	M5	74.03	M5	93.16		
	111.32		115.47		66.03		102.3		
	223.33		100.20		92.10		84.28		
M10	770.08	M10	619.42	M10	110.25	M10	184.2		
	766.16		456.41		306.50		362.56		
	491.50		557.0		59.25		78.35		
M2.5		M2.5		M2.5		M2.5			
P2.5	59.07	P2.5	79.4	P2.5	49.55	P2.5	37.75		
	38.62		50.03		41.96		42.30		
	93.37		44.74		43.63		40.58		
M10		M10		M10		M10			
P2.5	354.11	P2.5	71.50	P2.5	52.80	P2.5	60.31		
	98.25		79.25		43.95		86.70		
	392.61		92.37		47.16		173.38		
M2.5		M2.5		M2.5		M2.5			
P10	237.0	P10	310.85	P10	231.94	P10	250.77		
	1634.0		310.80		429.87		449.0		
	2596.0		333.60		270.52		153.47		
M5P5	126.29	M5P5	57.87	M5P5	34.93	M5P5	51.53		
	113.03		55.29		54.71		70.82		
	149.38		209.17		115.0		121.77		
M10		M10		M10		M10			
P10	81.21	P10	89.64	P10	254.9	P10	535.06		
	603.28		100.73		283.33		74.20		
	239.2		99.14		61.11		95.71		

LEGEND

C.M. = Control Mean

P = Pentobarbital

M = Methylphenidat

TABLE 2. RESPONSE RATE PER MINUTE

RAT I		RAT III		RAT IV		RAT V		MEAN	
C1	11.51	C1	5.05	C1	13.71	C1	22.42	C	17.36
2	12.45	2	8.90	2	14.65	2	19.71	P.5	15.91
3	18.40	3	15.71	3	11.88	3	27.53	P2.5	17.00
4	21.40	4	15.87	4	12.93	4	27.61	P5	11.95
5	18.23	5	12.57	5	19.25	5	21.24	P10	4.57
6	18.06	6	18.80	6	13.05	6	29.42	M.5	18.17
7	14.22	7	16.84	7	16.64	7	25.13	M2.5	19.33
8	16.62	8	16.13	8	14.88	8	27.82	M5	21.26
9	16.33	9	15.30	9	9.64	9	21.98	M10	13.00
10	12.37	10	14.10	10	20.15	10	26.00	M2.5	
C.M.=	15.96	C.M.=	13.92	C.M.=	14.68	C.M.=	24.86	P2.5	22.58
P.5	17.98	P.5	8.68	P.5	10.27	P.5	25.20	M10	
	19.99		6.52		15.51		16.38	P2.5	18.77
	18.72		13.01		15.39		23.26	M2.5	
P2.5	17.28	P2.5	8.44	P2.5	13.44	P2.5	20.68	P10	14.16
	17.01		10.96		21.98		17.02	M5P5	21.59
	17.80		17.05		23.04		23.02	M10	
P5	1.68	P5	4.20	P5	15.29	P5	15.24	P10	16.47
	11.94		5.47		15.57		15.36		
	11.11		15.27		13.02		19.21		
P10	6.69	P10	2.68	P10	15.34	P10	3.94		
	1.01		0.02		8.37		8.08		
	0.50		2.13		4.07		2.03		
M.5	15.88	M.5	18.99	M.5	34.74	M.5	17.29		
	12.17		17.96		8.77		16.99	LEGEND	
	20.29		14.61		16.49		23.70		
M2.5	18.84	M2.5	12.88	M2.5	18.19	M2.5	25.77	C.M. =	
	21.99		11.76		21.84		25.11	Control Mean	
	20.81		17.39		16.32		21.02	P =	
M5	21.57	M5	17.18	M5	31.48	M5	20.32	Pentobarbital	
	18.88		10.05		31.00		17.58	M =	
	16.74		9.98		35.99		24.37	Methylphenidate	
M10	7.36	M10	7.28	M10	17.82	M10	11.26		
	5.43		12.38		26.84		23.10		
	8.07		11.87		8.15		16.46		
M2.5		M2.5		M2.5		M2.5			
P2.5	19.61	P2.5	3.5	P2.5	25.60	P2.5	21.9		
	22.10		16.59		31.40		28.82		
	18.40		19.38		34.16		29.48		
M10		M10		M10		M10			
P2.5	16.20	P2 5	16.82	P2.5	45.80	P2.5	19.99		
	11.31		11.68		25.65		13.04		
	12.64		12.98		26.94		12.16		
M2.5		M2.5		M2.5		M2.5			
P10	6.4	P10	5.5	P10	84.00	P10	18.59		
	3.6		2.4		8.10		7.90		
	2.16		5.64		12.07		13.58		
M5P5	12.3	M5P5	14.8	M5P5	40.39	M5P5	26.80		
	18.60		10.0		25.50		30.42		
	16.90		11.04		25.89		26.46		
M10		M10		M10		M10			
P10	8.50	P10	11.89	P10	38.40	P10	19.90		
	13.00		10.99		25.30		19.70		
	4.64		8.40		20.50		16.40		

TABLE 3. POST-REINFORCEMENT PAUSING (in seconds)

RAT I		RAT III		RAT IV		RAT V		MEAN	
C1	171.75	C1	198.10	C1	172.48	C1	163.43	C	162.31
2	157.08	2	195.36	2	171.62	2	167.0	P.5	172.76
3	121.08	3	178.84	3	176.84	3	138.75	P2.5	167.09
4	89.63	4	179.21	4	176.14	4	154.22	P5	164.86
5	144.83	5	190.74	5	171.17	5	171.31	P10	112.92
6	141.82	6	173.27	6	159.85	6	146.95	M.5	164.12
7	157.89	7	174.39	7	157.94	7	157.15	M2.5	155.88
8	121.82	8	178.27	8	172.18	8	145.31	M5	125.10
9	153.16	9	181.29	9	183.63	9	153.01	M10	107.84
10	154.30	10	188.03	10	158.15	10	144.63	M2.5	
C.M.=141.34		C.M.=183.75		C.M.=170.00		C.M.=154.18		P2.5	141.17
P.5	135.01	P.5	199.88	P.5	190.31	P.5	158.95	M10	
	164.79		207.10		167.16		182.81	P2.5	120.79
	152.15		186.17		168.30		160.39	M2.5	
P2.5	157.50	P2.5	195.36	P2.5	174.31	P2.5	169.43	P10	168.96
	166.55		192.74		157.92		179.38	M5P5	146.14
	157.98		171.55		113.12		169.27	M10	
P5	152.75	P5	138.85	P5	163.97	P5	167.93	P10	147.54
	157.50		200.08		167.13		162.6		
	153.46		172.16		165.86		176.14		
P10	155.8	P10	154.5	P10	153.76	P10	162.87		
	41.5		0.0		161.45		135.8		
	0.0		135.66		133.70		120.0		
M.5	140.62	M.5	153.98	M.5	137.7	M.5	167.56		
	175.64		172.78		188.27		184.15		
	141.48		182.01		161.84		163.51		
M2.5	134.16	M2.5	186.77	M2.5	176.19	M2.5	148.78	LEGEND	
	123.17		184.38		157.20		151.68		
	130.29		163.24		170.52		144.22	C.M. =	
M5	92.62	M5	156.96	M5	118.08	M5	134.86	Control Mean	
	66.18		174.04		124.48		119.26	P =	
	113.02		171.81		95.55		134.27	Pentobarbital	
M10	83.0	M10	135.46	M10	75.62	M10	123.10	M =	
	54.62		137.81		114.28		104.80	Methylphenidate	
	125.18		129.07		126.96		84.23		
M2.5		M2.5		M2.5		M2.2			
P2.5	168.46	P2.5	14.32	P2.5	146.96	P2.5	159.35		
	156.87		171.55		147.28		144.01		
	127.01		171.80		136.70		149.73		
M10		M10		M10		M10			
P2.5	114.55	P2.5	133.0	P2.5	137.51	P2.5	130.40		
	140.40		149.81		95.31		125.12		
	104.64		120.53		99.26		98.95		
M2.5		M2.5		M2.5		M2.5			
P10	180.63	P10	165.85	P10	173.53	P10	146.45		
	168.5		169.10		161.73		189.68		
	170.37		176.75		157.45		167.58		
M5P5	181.95	M5P5	169.4	M5P5	125.6	M5P5	121.10		
	146.55		190.63		131.98		144.21		
	148.94		164.43		116.48		112.40		
M10		M10		M10		M10			
P10	125.89	P10	117.03	P10	94.04	P10	463.00		
	115.73		135.00		103.67		108.84		
	180.0		151.00		101.29		75.10		